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(54) Title: MODIFIED PEPTIDES AS THERAPEUTIC AGENTS

(57) Abstract

The present invention concerns fusion of Fc domains with biologically active peptides and a process for preparing pharmaceutical agents using biologically active peptides. In this invention, pharmacologically active compounds are prepared by a process comprising: a) selecting at least one peptide that modulates the activity of a protein of interest; and b) preparing a pharmacologic agent comprising an Fc domain covalently linked to at least one amino acid of the selected peptide. Linkage to the vehicle increases the half-life of the peptide, which otherwise would be quickly degraded in vivo. The preferred vehicle is an Fc domain. The peptide is preferably selected by phage display, E. coli display, ribosome display, RNA-peptide screening, or chemical-peptide screening.

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Modified Peptides as Therapeutic Agents Background of the Invention

Recombinant proteins are an emerging class of therapeutic agents. Such recombinant therapeutics have engendered advances in protein formulation and chemical modification. Such modifications can protect therapeutic proteins, primarily by blocking their exposure to proteolytic enzymes. Protein modifications may also increase the therapeutic protein's stability, circulation time, and biological activity. A review article describing protein modification and fusion proteins is Francis (1992), Focus on Growth Factors 3:4-10 (Mediscript, London), which is hereby incorporated by reference.

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One useful modification is combination with the "Fc" domain of an antibody. Antibodies comprise two functionally independent parts, a variable domain known as "Fab", which binds antigen, and a constant domain known as "Fc", which links to such effector functions as complement activation and attack by phagocytic cells. An Fc has a long serum half-life, whereas an Fab is short-lived. Capon et al. (1989), Nature 337: 525-31. When constructed together with a therapeutic protein, an Fc domain can provide longer half-life or incorporate such functions as Fc receptor binding, protein A binding, complement fixation and perhaps even placental transfer. Id. Table 1 summarizes use of Fc fusions known in the art.

Table 1—Fc fusion with therapeutic proteins

Form of Fc	Fusion	Therapeutic	
	partner	implications	Reference
lgG1	N-terminus of CD30-L	Hodgkin's disease; anaplastic lymphoma; T- cell leukemia	U.S. Patent No. 5,480,981
Murine Fcγ2a	IL-10	anti-inflammatory; transplant rejection	Zheng <u>et al</u> . (1995), <u>J.</u> <u>Immunol</u> . 154: 5590-600
lgG1	TNF receptor	septic shock	Fisher <u>et al.</u> (1996), <u>N.</u> <u>Engl. J. Med.</u> 334: 1697- 1702; Van Zee, K. <u>et al.</u> (1996), <u>J. Immunol.</u> 156: 2221-30
IgG, IgA, IgM, or IgE (excluding the first domain)	TNF receptor	inflammation, autoimmune disorders	U.S. Pat. No. 5,808,029, issued September 15, 1998
lgG1	CD4 receptor	AIDS	Capon <u>et al.</u> (1989), <u>Nature 337</u> : 525-31
lgG1, lgG3	N-terminus of IL-2	anti-cancer, antiviral	Harvill <u>et al.</u> (1995), <u>Immunotech</u> . 1: 95-105
lgG1	C-terminus of OPG	osteoarthritis; bone density	WO 97/23614, published July 3, 1997
lgG1	N-terminus of leptin	anti-obesity	PCT/US 97/23183, filed December 11, 1997
Human Ig Cγ1	CTLA-4	autoimmune disorders	Linsley (1991), <u>J. Exp.</u> <u>Med</u> . 174:561-9

A much different approach to development of therapeutic agents is peptide library screening. The interaction of a protein ligand with its receptor often takes place at a relatively large interface. However, as demonstrated for human growth hormone and its receptor, only a few key residues at the interface contribute to most of the binding energy. Clackson et al. (1995), Science 267: 383-6. The bulk of the protein ligand merely displays the binding epitopes in the right topology or serves functions unrelated to binding. Thus, molecules of only "peptide" length (2 to 40 amino acids) can bind to the receptor protein of a given large protein ligand. Such peptides may mimic the bioactivity of the large protein ligand ("peptide agonists") or, through competitive binding, inhibit the bioactivity of the large protein ligand ("peptide antagonists").

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Phage display peptide libraries have emerged as a powerful method in identifying such peptide agonists and antagonists. See, for example, Scott et al. (1990), Science 249: 386; Devlin et al. (1990), Science 249: 404; U.S. Pat. No. 5,223,409, issued June 29, 1993; U.S. Pat. No. 5,733,731, issued March 31, 1998; U.S. Pat. No. 5,498,530, issued March 12, 1996; U.S. Pat. No. 5,432,018, issued July 11, 1995; U.S. Pat. No. 5,338,665, issued August 16, 1994; U.S. Pat. No. 5,922,545, issued July 13, 1999; WO 96/40987, published December 19, 1996; and WO 98/15833, published April 16, 1998 (each of which is incorporated by reference). In such libraries, random peptide sequences are displayed by fusion with coat proteins of filamentous phage. Typically, the displayed peptides are affinity-eluted against an antibody-immobilized extracellular domain of a receptor. The retained phages may be enriched by successive rounds of affinity purification and repropagation. The best binding peptides may be sequenced to identify key residues within one or more structurally related families of peptides. See, e.g., Cwirla et al. (1997), Science 276: 1696-9, in which two distinct families were identified. The peptide sequences may also suggest which residues may be safely replaced by alanine scanning or by mutagenesis at the DNA level. Mutagenesis libraries may be created and screened to further optimize the sequence of the best binders. Lowman (1997), Ann. Rev. Biophys. Biomol. Struct. 26: 401-24.

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Structural analysis of protein-protein interaction may also be used to suggest peptides that mimic the binding activity of large protein ligands. In such an analysis, the crystal structure may suggest the identity and relative orientation of critical residues of the large protein ligand, from which a peptide may be designed. See, e.g., Takasaki et al. (1997), Nature Biotech. 15: 1266-70. These analytical methods may also be used to investigate the interaction between a receptor protein and peptides

selected by phage display, which may suggest further modification of the peptides to increase binding affinity.

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Other methods compete with phage display in peptide research. A peptide library can be fused to the carboxyl terminus of the lac repressor and expressed in E. coli. Another E. coli-based method allows display on the cell's outer membrane by fusion with a peptidoglycan-associated lipoprotein (PAL). Hereinafter, these and related methods are collectively referred to as "E. coli display." In another method, translation of random RNA is halted prior to ribosome release, resulting in a library of polypeptides with their associated RNA still attached. Hereinafter, this and related methods are collectively referred to as "ribosome display." Other methods employ chemical linkage of peptides to RNA; see, for example, Roberts & Szostak (1997), Proc. Natl. Acad. Sci. USA, 94: 12297-303. Hereinafter, this and related methods are collectively referred to as "RNA-peptide screening." Chemically derived peptide libraries have been developed in which peptides are immobilized on stable, non-biological materials, such as polyethylene rods or solvent-permeable resins. Another chemically derived peptide library uses photolithography to scan peptides immobilized on glass slides. Hereinafter, these and related methods are collectively referred to as "chemical-peptide screening." Chemical-peptide screening may be advantageous in that it allows use of D-amino acids and other unnatural analogues, as well as non-peptide elements. Both biological and chemical methods are reviewed in Wells & Lowman (1992), Curr. Opin. Biotechnol. 3: 355-62.

Conceptually, one may discover peptide mimetics of any protein using phage display and the other methods mentioned above. These methods have been used for epitope mapping, for identification of critical amino acids in protein-protein interactions, and as leads for the discovery of new therapeutic agents. E.g., Cortese et al. (1996), Curr. Opin. Biotech. 7:

616-21. Peptide libraries are now being used most often in immunological studies, such as epitope mapping. Kreeger (1996), <u>The Scientist</u> 10(13): 19-20.

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Of particular interest here is use of peptide libraries and other techniques in the discovery of pharmacologically active peptides. A number of such peptides identified in the art are summarized in Table 2. The peptides are described in the listed publications, each of which is hereby incorporated by reference. The pharmacologic activity of the peptides is described, and in many instances is followed by a shorthand term therefor in parentheses. Some of these peptides have been modified (e.g., to form C-terminally cross-linked dimers). Typically, peptide libraries were screened for binding to a receptor for a pharmacologically active protein (e.g., EPO receptor). In at least one instance (CTLA4), the peptide library was screened for binding to a monclonal antibody.

Table 2—Pharmacologically active peptides

Form of peptide	Binding partner/ protein of interest*	Pharmacologic activity	Reference
intrapeptide disulfide- bonded	EPO receptor	EPO-mimetic	Wrighton <u>et al</u> . (1996), <u>Science</u> 273: 458-63; U.S. Pat. No. 5,773,569, issued June 30, 1998 to Wrighton <u>et al</u> .
C-terminally cross-linked dimer	EPO receptor	EPO-mimetic	Livnah <u>et al</u> . (1996), <u>Science</u> 273: 464-71; Wrighton <u>et al</u> . (1997), <u>Nature Biotechnology</u> 15 1261-5; International patent application WO 96/40772, published Dec. 19, 1996
linear	EPO receptor	EPO-mimetic	Naranda <u>et al</u> . (1999), <u>Proc. Natl. Acad. Sci.</u> <u>USA</u> , 96: 7569-74
linear	c-Mpl	TPO-mimetic	Cwirla et al.(1997) Science 276: 1696-9; U.S. Pat. No. 5,869,451 issued Feb. 9, 1999; U.S. Pat. No. 5,932,946, issued Aug. 3, 1999
C-terminally cross-linked dimer	c-MpI	TPO-mimetic	Cwirla <u>et al.</u> (1997), <u>Science</u> 276: 1696-9
disulfide- linked dimer		stimulation of hematopoiesis ("G-CSF-mimetic")	Paukovits <u>et al</u> . (1984), <u>Hoppe-Seylers Z.</u> <u>Physiol. Chem</u> . 365: 30: 11; Laerum <u>et al</u> . (1988) <u>Exp. Hemat</u> . 16: 274-80
alkylene- linked dimer		G-CSF-mimetic	Bhatnagar <u>et al</u> . (1996), J. Med. Chem. 39: 3814 9; Cuthbertson <u>et al</u> . (1997), J. Med. Chem. 40: 2876-82; King <u>et al</u> . (1991), <u>Exp. Hematol</u> . 19:481; King <u>et al</u> . (1995), <u>Blood</u> 86 (Supp 1): 309a
linear	IL-1 receptor	inflammatory and autoimmune diseases ("IL-1 antagonist" or "IL-1 ra-mimetic")	U.S. Pat. No. 5,608,035 U.S. Pat. No. 5,786,33 U.S. Pat. No. 5,880,090 Yanofsky et al. (1996),

^a The protein listed in this column may be bound by the associated peptide (e.g., EPO receptor, IL-1 receptor) or mimicked by the associated peptide. The references listed for each clarify whether the molecule is bound by or mimicked by the peptides.

			Proc. Natl. Acad. Sci. 93: 7381-6; Akeson et al. (1996), J. Biol. Chem. 271: 30517-23; Wiekzorek et al. (1997), Pol. J. Pharmacol. 49: 107-17; Yanofsky (1996), PNAs, 93:7381-7386.
linear	Facteur thymique serique (FTS)	stimulation of lymphocytes ("FTS-mimetic")	Inagaki-Ohara et al. (1996), <u>Cellular Immunol</u> . 171: 30-40; Yoshida (1984), Int. J. Immunopharmacol, 6:141-6.
intrapeptide disulfide bonded	CTLA4 MAb	CTLA4-mimetic	Fukumoto <u>et al.</u> (1998), Nature Biotech. 16: 267- 70
exocyclic	TNF-α receptor	TNF- α antagonist	Takasaki <u>et al</u> . (1997), <u>Nature Biotech</u> . 15:1266- 70; WO 98/53842, published December 3, 1998
linear	TNF-α receptor	TNF-α antagonist	Chirinos-Rojas (), <u>J.</u> <u>Imm.</u> , 5621-5626.
intrapeptide disulfide bonded	C3b	inhibition of complement activation; autoimmune diseases ("C3b-antagonist")	Sahu <u>et al</u> . (1996), <u>J.</u> <u>Immunol</u> . 157: 884-91; Morikis <u>et al</u> . (1998), <u>Protein Sci</u> . 7: 619-27
linear	vinculin	cell adhesion processes— cell growth, differentiation, wound healing, tumor metastasis ("vinculin binding")	Adey <u>et al</u> . (1997), <u>Biochem. J</u> . 324: 523-8
linear	C4 binding protein (C4BP)	anti-thrombotic	Linse <u>et al</u> . (1997), <u>J.</u> <u>Biol. Chem</u> . 272: 14658- 65
linear	urokinase receptor	processes associated with urokinase interaction with its receptor (e.g., angiogenesis, tumor cell invasion and metastasis); ("UKR antagonist")	Goodson et al. (1994), Proc. Natl. Acad. Sci. 91: 7129-33; International application WO 97/35969, published October 2, 1997
linear	Mdm2, Hdm2	Inhibition of inactivation of p53 mediated by Mdm2 or hdm2; anti-tumor ("Mdm/hdm antagonist")	Picksley <u>et al</u> . (1994), <u>Oncogene</u> 9: 2523-9; Bottger <u>et al</u> . (1997) <u>J.</u> <u>Mol. Biol</u> . 269: 744-56; Bottger <u>et al</u> . (1996), <u>Oncogene</u> 13: 2141-7
linear	p21 ^{WAF1}	anti-tumor by mimicking the activity of p21 waft	Ball et al. (1997), <u>Curr.</u> Biol. 7: 71-80
linear	farnesyl	anti-cancer by preventing	Gibbs et al. (1994), <u>Cell</u>

^b FTS is a thymic hormone mimicked by the molecule of this invention rather than a receptor bound by the molecule of this invention.

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	transferase	activation of ras oncogene	77:175-178
linear	Ras effector domain	anti-cancer by inhibiting biological function of the ras oncogene	Moodie et al. (1994), <u>Trends Genet</u> 10: 44-48 Rodriguez et al. (1994), <u>Nature</u> 370:527-532
linear	SH2/SH3 domains	anti-cancer by inhibiting tumor growth with activated tyrosine kinases	Pawson et al (1993), <u>Curr. Biol.</u> 3:434-432 Yu et al. (1994), <u>Cell</u> 76:933-945
linear	p16 ^{INK4}	anti-cancer by mimicking activity of p16; e.g., inhibiting cyclin D-Cdk complex ("p16-mimetic")	Fåhraeus <u>et al</u> . (1996), <u>Curr, Biol</u> . 6:84-91
linear	Src, Lyn	inhibition of Mast cell activation, IgE-related conditions, type I hypersensitivity ("Mast cell antagonist")	Stauffer <u>et al</u> . (1997), <u>Biochem</u> . 36: 9388-94
linear	Mast cell protease	treatment of inflammatory disorders mediated by release of tryptase-6 ("Mast cell protease inhibitors")	International application WO 98/33812, published August 6, 1998
linear	SH3 domains	treatment of SH3- mediated disease states ("SH3 antagonist")	Rickles <u>et al</u> . (1994), <u>EMBO J</u> . 13: 5598-5604; Sparks <u>et al</u> . (1994), <u>J</u> . <u>Biol, Chem</u> . 269: 23853- 6; Sparks <u>et al</u> . (1996), <u>Proc. Natl. Acad. Sci</u> . 93: 1540-4
linear	HBV core antigen (HBcAg)	treatment of HBV viral infections ("anti-HBV")	Dyson & Muray (1995), Proc. Natl. Acad. Sci. 92: 2194-8
linear	selectins	neutrophil adhesion; inflammatory diseases ("selectin antagonist")	Martens et al. (1995), J. Biol. Chem. 270: 21129-36; European patent application EP 0 714 912, published June 5, 1996
linear, cyclized	calmodulin	calmodulin antagonist	Pierce et al. (1995), Molec. Diversity 1: 259- 65; Dedman et al. (1993), J. Biol. Chem. 268: 23025-30; Adey & Kay (1996), Gene 169: 133-4
linear, cyclized-	integrins	tumor-homing; treatment for conditions related to integrin-mediated cellular events, including platelet aggregation, thrombosis, wound healing, osteoporosis, tissue repair, angiogenesis (e.g.	International applications WO 95/14714, published June 1, 1995; WO 97/08203, published March 6, 1997; WO 98/10795, published March 19, 1998; WO 99/24462, published Ma

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		for treatment of cancer), and tumor invasion ("integrin-binding")	20, 1999; Kraft <u>et al</u> . (1999), J. Biol. Chem. 274: 1979-1985
cyclic, linear	fibronectin and extracellular matrix	treatment of inflammatory and autoimmune conditions	WO 98/09985, published March 12, 1998
	components of T cells and macrophages		
linear	somatostatin and cortistatin	treatment or prevention of hormone-producing tumors, acromegaly, giantism, dementia, gastric ulcer, tumor growth, inhibition of hormone secretion, modulation of sleep or neural activity	European patent application 0 911 393, published April 28, 1999
linear	bacterial lipopolysac- charide	antibiotic; septic shock; disorders modulatable by CAP37	U.S. Pat. No. 5,877,151, issued March 2, 1999
linear or cyclic, including D-	pardaxin, mellitin	antipathogenic	WO 97/31019, published 28 August 1997
amino acids linear, cyclic	VIP	impotence, neurodegenerative disorders	WO 97/40070, published October 30, 1997
linear	CTLs	cancer	EP 0 770 624, published May 2, 1997
linear	THF-gamma2		Burnstein (1988), Biochem., 27:4066-71.
linear	Amylin		Cooper (1987), <u>Proc.</u> Natl. Acad. Sci., 84:8628-32.
linear	Adrenomedullin		Kitamura (1993), <u>BBRC</u> , 192:553-60.
cyclic, linear	VEGF	anti-angiogenic; cancer, rheumatoid arthritis, diabetic retinopathy, psoriasis ("VEGF antagonist")	Fairbrother (1998), Biochem., 37:17754- 17764.
cyclic	ММР	inflammation and autoimmune disorders; tumor growth ("MMP inhibitor")	Koivunen (1999), Nature Biotech., 17:768-774.
	HGH fragment		U.S. Pat. No. 5,869,452
	Echistatin	inhibition of platelet aggregation	Gan (1988), <u>J. Biol.</u> Chem., 263:19827-32.
linear	SLE autoantibody	SLE	WO 96/30057, publisher October 3, 1996
	GD1alpha	suppression of tumor metastasis	Ishikawa et al. (1998), FEBS Lett. 441 (1): 20-
	antiphospholipid		, Blank <u>et al</u> . (1999), <u>Proc</u>
		C.	

	beta-2- glycoprotein-I (β2GPI) antibodies	antiphospholipid syndrome (APS), thromboembolic phenomena, thrombocytopenia, and recurrent fetal loss	Natl. Acad. Sci. USA 96: 5164-8
linear	T Cell Receptor beta chain	diabetes	WO 96/11214, published April 18, 1996

Peptides identified by peptide library screening have been regarded as "leads" in development of therapeutic agents rather than as therapeutic agents themselves. Like other proteins and peptides, they would be rapidly removed in vivo either by renal filtration, cellular clearance mechanisms in the reticuloendothelial system, or proteolytic degradation. Francis (1992), Focus on Growth Factors 3: 4-11. As a result, the art presently uses the identified peptides to validate drug targets or as scaffolds for design of organic compounds that might not have been as easily or as quickly identified through chemical library screening. Lowman (1997), Ann. Rev. Biophys. Biomol. Struct. 26: 401-24; Kay et al. (1998), Drug Disc. Today 3: 370-8. The art would benefit from a process by which such peptides could more readily yield therapeutic agents.

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Summary of the Invention

The present invention concerns a process by which the <u>in vivo</u> halflife of one or more biologically active peptides is increased by fusion with a vehicle. In this invention, pharmacologically active compounds are prepared by a process comprising:

- selecting at least one peptide that modulates the activity of a protein of interest; and
- b) preparing a pharmacologic agent comprising at least one vehicle covalently linked to at least one amino acid sequence of the selected peptide.

The preferred vehicle is an Fc domain. The peptides screened in step (a) are preferably expressed in a phage display library. The vehicle and the

peptide may be linked through the N- or C-terminus of the peptide or the vehicle, as described further below. Derivatives of the above compounds (described below) are also encompassed by this invention.

The compounds of this invention may be prepared by standard synthetic methods, recombinant DNA techniques, or any other methods of preparing peptides and fusion proteins. Compounds of this invention that encompass non-peptide portions may be synthesized by standard organic chemistry reactions, in addition to standard peptide chemistry reactions when applicable.

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The primary use contemplated is as therapeutic or prophylactic agents. The vehicle-linked peptide may have activity comparable to—or even greater than—the natural ligand mimicked by the peptide. In addition, certain natural ligand-based therapeutic agents might induce antibodies against the patient's own endogenous ligand; the vehicle-linked peptide avoids this pitfall by having little or typically no sequence identity with the natural ligand.

Although mostly contemplated as therapeutic agents, compounds of this invention may also be useful in screening for such agents. For example, one could use an Fc-peptide (e.g., Fc-SH2 domain peptide) in an assay employing anti-Fc coated plates. The vehicle, especially Fc, may make insoluble peptides soluble and thus useful in a number of assays.

The compounds of this invention may be used for therapeutic or prophylactic purposes by formulating them with appropriate pharmaceutical carrier materials and administering an effective amount to a patient, such as a human (or other mammal) in need thereof. Other related aspects are also included in the instant invention.

Numerous additional aspects and advantages of the present invention will become apparent upon consideration of the figures and detailed description of the invention.

Brief Description of the Figures

Figure 1 shows a schematic representation of an exemplary process of the invention. In this preferred process, the vehicle is an Fc domain, which is linked to the peptide covalently by expression from a DNA construct encoding both the Fc domain and the peptide. As noted in Figure 1, the Fc domains spontaneously form a dimer in this process.

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Figure 2 shows exemplary Fc dimers that may be derived from an IgG1 antibody. "Fc" in the figure represents any of the Fc variants within the meaning of "Fc domain" herein. "X¹" and "X²" represent peptides or linker-peptide combinations as defined hereinafter. The specific dimers are as follows:

A, D: Single disulfide-bonded dimers. IgG1 antibodies typically have two disulfide bonds at the hinge region between the constant and variable domains. The Fc domain in Figures 2A and 2 D may be formed by truncation between the two disulfide bond sites or by substitution of a cysteinyl residue with an unreactive residue (e.g., alanyl). In Figure 2A, the Fc domain is linked at the amino terminus of the peptides; in 2D, at the carboxyl terminus.

B, E: Doubly disulfide-bonded dimers. This Fc domain may be formed by truncation of the parent antibody to retain both cysteinyl residues in the Fc domain chains or by expression from a construct including a sequence encoding such an Fc domain. In Figure 2B, the Fc domain is linked at the amino terminus of the peptides; in 2E, at the carboxyl terminus.

C, F: Noncovalent dimers. This Fc domain may be formed by elimination of the cysteinyl residues by either truncation or substitution.

One may desire to eliminate the cysteinyl residues to avoid impurities formed by reaction of the cysteinyl residue with cysteinyl residues of other

proteins present in the host cell. The noncovalent bonding of the Fc domains is sufficient to hold together the dimer.

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Other dimers may be formed by using Fc domains derived from different types of antibodies (e.g., IgG2, IgM).

Figure 3 shows the structure of preferred compounds of the invention that feature tandem repeats of the pharmacologically active peptide. Figure 3A shows a single chain molecule and may also represent the DNA construct for the molecule. Figure 3B shows a dimer in which the linker-peptide portion is present on only one chain of the dimer. Figure 3C shows a dimer having the peptide portion on both chains. The dimer of Figure 3C will form spontaneously in certain host cells upon expression of a DNA construct encoding the single chain shown in Figure 3A. In other host cells, the cells could be placed in conditions favoring formation of dimers or the dimers can be formed in vitro.

Figure 4 shows exemplary nucleic acid and amino acid sequences (SEQ ID NOS: 1 and 2, respectively) of human IgG1 Fc that may be used in this invention.

Figure 5 shows a synthetic scheme for the preparation of PEGylated peptide 19 (SEQ ID NO: 3).

Figure 6 shows a synthetic scheme for the preparation of PEGylated peptide 20 (SEQ ID NO: 4).

Figure 7 shows the nucleotide and amino acid sequences (SEQ ID NOS: 5 and 6, respectively) of the molecule identified as "Fc-TMP" in Example 2 hereinafter.

Figure 8 shows the nucleotide and amino acid sequences (SEQ. ID. NOS: 7 and 8, respectively) of the molecule identified as "Fc-TMP-TMP" in Example 2 hereinafter.

Figure 9 shows the nucleotide and amino acid sequences (SEQ. ID. NOS: 9 and 10, respectively) of the molecule identified as "TMP-TMP-Fc" in Example 2 hereinafter.

Figure 10 shows the nucleotide and amino acid sequences (SEQ. ID. NOS: 11 and 12, respectively) of the molecule identified as "TMP-Fc" in Example 2 hereinafter.

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Figure 11 shows the number of platelets generated <u>in vivo</u> in normal female BDF1 mice treated with one 100 μ g/kg bolus injection of various compounds, with the terms defined as follows.

PEG-MGDF: 20 kD average molecular weight PEG attached by reductive amination to the N-terminal amino group of amino acids 1-163 of native human TPO, which is expressed in <u>E. coli</u> (so that it is not glycosylated);

TMP: the TPO-mimetic peptide having the amino acid sequence IEGPTLRQWLAARA (SEQ ID NO: 13);

TMP-TMP: the TPO-mimetic peptide having the amino acid sequence IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA (SEQ ID NO: 14);

PEG-TMP-TMP: the peptide of SEQ ID NO: 14, wherein the PEG group is a 5 kD average molecular weight PEG attached as shown in Figure 6;

Fc-TMP-TMP: the compound of SEQ ID NO: 8 (Figure 8) dimerized with an identical second monomer (i.e., Cys residues 7 and 10 are bound to the corresponding Cys residues in the second monomer to form a dimer, as shown in Figure 2); and

TMP-TMP-Fc is the compound of SEQ ID NO: 10 (Figure 9)
dimerized in the same way as TMP-TMP-Fc except that the Fc
domain is attached at the C-terminal end rather than the Nterminal end of the TMP-TMP peptide.

Figure 12 shows the number of platelets generated <u>in vivo</u> in normal BDF1 mice treated with various compounds delivered via implanted osmotic pumps over a 7-day period. The compounds are as defined for Figure 7.

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Figure 13 shows the nucleotide and amino acid sequences (SEQ. ID. NOS: 15 and 16, respectively) of the molecule identified as "Fc-EMP" in Example 3 hereinafter.

Figure 14 shows the nucleotide and amino acid sequences (SEQ ID NOS: 17 and 18, respectively) of the molecule identified as "EMP-Fc" in Example 3 hereinafter.

Figure 15 shows the nucleotide and amino acid sequences (SEQ ID NOS:19 and 20, respectively) of the molecule identified as "EMP-EMP-Fc" in Example 3 hereinafter.

Figure 16 shows the nucleotide and amino acid sequences (SEQ ID NOS: 21 and 22, respectively) of the molecule identified as "Fc-EMP-EMP" in Example 3 hereinafter.

Figures 17A and 17B show the DNA sequence (SEQ ID NO: 23) inserted into pCFM1656 between the unique <u>Aat</u>II (position #4364 in pCFM1656) and <u>Sac</u>II (position #4585 in pCFM1656) restriction sites to form expression plasmid pAMG21 (ATCC accession no. 98113).

Figure 18A shows the hemoglobin, red blood cells, and hematocrit generated in vivo in normal female BDF1 mice treated with one 100 μ g/kg bolus injection of various compounds. Figure 18B shows the same results with mice treated with 100 μ g/kg per day delivered the same dose by 7-day micro-osmotic pump with the EMPs delivered at 100 μ g/kg, rhEPO at 30U/mouse. (In both experiments, neutrophils, lymphocytes, and platelets were unaffected.) In these figures, the terms are defined as follows.

Fc-EMP: the compound of SEQ ID NO: 16 (Figure 13) dimerized with an identical second monomer (i.e., Cys residues 7 and 10 are

bound to the corresponding Cys residues in the second monomer to form a dimer, as shown in Figure 2);

EMP-Fc: the compound of SEQ ID NO: 18 (Figure 14) dimerized in the same way as Fc-EMP except that the Fc domain is attached at the C-terminal end rather than the N-terminal end of the EMP peptide.

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"EMP-EMP-Fc" refers to a tandem repeat of the same peptide (SEQ ID NO: 20) attached to the same Fc domain by the carboxyl terminus of the peptides. "Fc-EMP-EMP" refers to the same tandem repeat of the peptide but with the same Fc domain attached at the amino terminus of the tandem repeat. All molecules are expressed in <u>E. coli</u> and so are not glycosylated.

Figures 19A and 19B show the nucleotide and amino acid sequences (SEQ ID NOS: 1055 and 1056) of the Fc-TNF- α inhibitor fusion molecule described in Example 4 hereinafter.

Figures 20A and 20B show the nucleotide and amino acid sequences (SEQ ID NOS: 1057 and 1058) of the TNF- α inhibitor-Fc fusion molecule described in Example 4 hereinafter.

Figures 21A and 21B show the nucleotide and amino acid sequences (SEQ ID NOS: 1059 and 1060) of the Fc-IL-1 antagonist fusion molecule described in Example 5 hereinafter.

Figures 22A and 22B show the nucleotide and amino acid sequences (SEQ ID NOS: 1061 and 1062) of the IL-1 antagonist-Fc fusion molecule described in Example 5 hereinafter.

Figures 23A, 23B, and 23C show the nucleotide and amino acid sequences (SEQ ID NOS: 1063 and 1064) of the Fc-VEGF antagonist fusion molecule described in Example 6 hereinafter.

Figures 24A and 24B show the nucleotide and amino acid sequences (SEQ ID NOS: 1065 and 1066) of the VEGF antagonist-Fc fusion molecule described in Example 6 hereinafter.

Figures 25A and 25B show the nucleotide and amino acid sequences (SEQ ID NOS: 1067 and 1068) of the Fc-MMP inhibitor fusion molecule described in Example 7 hereinafter.

Figures 26A and 26B show the nucleotide and amino acid sequences (SEQ ID NOS: 1069 and 1070) of the MMP inhibitor-Fc fusion molecule described in Example 7 hereinafter.

Detailed Description of the Invention

Definition of Terms

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The terms used throughout this specification are defined as follows, unless otherwise limited in specific instances.

The term "comprising" means that a compound may include additional amino acids on either or both of the N- or C- termini of the given sequence. Of course, these additional amino acids should not significantly interfere with the activity of the compound.

The term "vehicle" refers to a molecule that prevents degradation and/or increases half-life, reduces toxicity, reduces immunogenicity, or increases biological activity of a therapeutic protein. Exemplary vehicles include an Fc domain (which is preferred) as well as a linear polymer (e.g., polyethylene glycol (PEG), polylysine, dextran, etc.); a branched-chain polymer (see, for example, U.S. Patent No. 4,289,872 to Denkenwalter et al., issued September 15, 1981; 5,229,490 to Tam, issued July 20, 1993; WO 93/21259 by Frechet et al., published 28 October 1993); a lipid; a cholesterol group (such as a steroid); a carbohydrate or oligosaccharide; or any natural or synthetic protein, polypeptide or peptide that binds to a salvage receptor. Vehicles are further described hereinafter.

The term "native Fc" refers to molecule or sequence comprising the sequence of a non-antigen-binding fragment resulting from digestion of whole antibody, whether in monomeric or multimeric form. The original immunoglobulin source of the native Fc is preferably of human origin and may be any of the immunoglobulins, although IgG1 and IgG2 are preferred. Native Fc's are made up of monomeric polypeptides that may be linked into dimeric or multimeric forms by covalent (i.e., disulfide bonds) and non-covalent association. The number of intermolecular disulfide bonds between monomeric subunits of native Fc molecules ranges from 1 to 4 depending on class (e.g., IgG, IgA, IgE) or subclass (e.g., IgG1, IgG2, IgG3, IgA1, IgGA2). One example of a native Fc is a disulfide-bonded dimer resulting from papain digestion of an IgG (see Ellison et al. (1982), Nucleic Acids Res. 10: 4071-9). The term "native Fc" as used herein is generic to the monomeric, dimeric, and multimeric forms.

The term "Fc variant" refers to a molecule or sequence that is modified from a native Fc but still comprises a binding site for the salvage receptor, FcRn. International applications WO 97/34631 (published 25 September 1997) and WO 96/32478 describe exemplary Fc variants, as well as interaction with the salvage receptor, and are hereby incorporated by reference. Thus, the term "Fc variant" comprises a molecule or sequence that is humanized from a non-human native Fc. Furthermore, a native Fc comprises sites that may be removed because they provide structural features or biological activity that are not required for the fusion molecules of the present invention. Thus, the term "Fc variant" comprises a molecule or sequence that lacks one or more native Fc sites or residues that affect or are involved in (1) disulfide bond formation, (2) incompatibility with a selected host cell (3) N-terminal heterogeneity upon expression in a selected host cell, (4) glycosylation, (5) interaction with complement, (6) binding to an Fc receptor other than a salvage receptor, or

(7) antibody-dependent cellular cytotoxicity (ADCC). Fc variants are described in further detail hereinafter.

The term "Fc domain" encompasses native Fc and Fc variant molecules and sequences as defined above. As with Fc variants and native Fc's, the term "Fc domain" includes molecules in monomeric or multimeric form, whether digested from whole antibody or produced by other means.

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The term "multimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two or more polypeptide chains associated covalently, noncovalently, or by both covalent and non-covalent interactions. IgG molecules typically form dimers; IgM, pentamers; IgD, dimers; and IgA, monomers, dimers, trimers, or tetramers. Multimers may be formed by exploiting the sequence and resulting activity of the native Ig source of the Fc or by derivatizing (as defined below) such a native Fc.

The term "dimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two polypeptide chains associated covalently or non-covalently. Thus, exemplary dimers within the scope of this invention are as shown in Figure 2.

The terms "derivatizing" and "derivative" or "derivatized" comprise processes and resulting compounds respectively in which (1) the compound has a cyclic portion; for example, cross-linking between cysteinyl residues within the compound; (2) the compound is cross-linked or has a cross-linking site; for example, the compound has a cysteinyl residue and thus forms cross-linked dimers in culture or in vivo; (3) one or more peptidyl linkage is replaced by a non-peptidyl linkage; (4) the N-terminus is replaced by -NRR¹, NRC(O)R¹, -NRC(O)OR¹, -NRS(O)₂R¹, -NHC(O)NHR, a succinimide group, or substituted or unsubstituted benzyloxycarbonyl-NH-, wherein R and R¹ and the ring substituents are

as defined hereinafter; (5) the C-terminus is replaced by -C(O)R² or -NR³R⁴ wherein R², R³ and R⁴ are as defined hereinafter; and (6) compounds in which individual amino acid moieties are modified through treatment with agents capable of reacting with selected side chains or terminal residues. Derivatives are further described hereinafter.

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The term "peptide" refers to molecules of 2 to 40 amino acids, with molecules of 3 to 20 amino acids preferred and those of 6 to 15 amino acids most preferred. Exemplary peptides may be randomly generated by any of the methods cited above, carried in a peptide library (e.g., a phage display library), or derived by digestion of proteins.

The term "randomized" as used to refer to peptide sequences refers to fully random sequences (e.g., selected by phage display methods) and sequences in which one or more residues of a naturally occurring molecule is replaced by an amino acid residue not appearing in that position in the naturally occurring molecule. Exemplary methods for identifying peptide sequences include phage display, <u>E. coli</u> display, ribosome display, RNA-peptide screening, chemical screening, and the like.

The term "pharmacologically active" means that a substance so described is determined to have activity that affects a medical parameter (e.g., blood pressure, blood cell count, cholesterol level) or disease state (e.g., cancer, autoimmune disorders). Thus, pharmacologically active peptides comprise agonistic or mimetic and antagonistic peptides as defined below.

The terms "-mimetic peptide" and "-agonist peptide" refer to a peptide having biological activity comparable to a protein (e.g., EPO, TPO, G-CSF) that interacts with a protein of interest. These terms further include peptides that indirectly mimic the activity of a protein of interest, such as by potentiating the effects of the natural ligand of the protein of interest; see, for example, the G-CSF-mimetic peptides listed in Tables 2

and 7. Thus, the term "EPO-mimetic peptide" comprises any peptides that can be identified or derived as described in Wrighton et al. (1996), Science 273: 458-63, Naranda et al. (1999), Proc. Natl. Acad. Sci. USA 96: 7569-74, or any other reference in Table 2 identified as having EPO-mimetic subject matter. Those of ordinary skill in the art appreciate that each of these references enables one to select different peptides than actually disclosed therein by following the disclosed procedures with different peptide libraries.

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The term "TPO-mimetic peptide" comprises peptides that can be identified or derived as described in Cwirla et al. (1997), Science 276: 1696-9, U.S. Pat. Nos. 5,869,451 and 5,932,946 and any other reference in Table 2 identifed as having TPO-mimetic subject matter, as well as the U.S. patent application, "Thrombopoietic Compounds," filed on even date herewith and hereby incorporated by reference. Those of ordinary skill in the art appreciate that each of these references enables one to select different peptides than actually disclosed therein by following the disclosed procedures with different peptide libraries.

The term "G-CSF-mimetic peptide" comprises any peptides that can be identified or described in Paukovits et al. (1984), <u>Hoppe-Seylers Z. Physiol. Chem.</u> 365: 303-11 or any of the references in Table 2 identified as having G-CSF-mimetic subject matter. Those of ordinary skill in the art appreciate that each of these references enables one to select different peptides than actually disclosed therein by following the disclosed procedures with different peptide libraries.

The term "CTLA4-mimetic peptide" comprises any peptides that can be identified or derived as described in Fukumoto et al. (1998), Nature Biotech. 16: 267-70. Those of ordinary skill in the art appreciate that each of these references enables one to select different peptides than actually

disclosed therein by following the disclosed procedures with different peptide libraries.

The term "-antagonist peptide" or "inhibitor peptide" refers to a peptide that blocks or in some way interferes with the biological activity of the associated protein of interest, or has biological activity comparable to a known antagonist or inhibitor of the associated protein of interest. Thus, the term "TNF-antagonist peptide" comprises peptides that can be identified or derived as described in Takasaki et al. (1997), Nature Biotech. 15: 1266-70 or any of the references in Table 2 identified as having TNF-antagonistic subject matter. Those of ordinary skill in the art appreciate that each of these references enables one to select different peptides than actually disclosed therein by following the disclosed procedures with different peptide libraries.

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The terms "IL-1 antagonist" and "IL-1ra-mimetic peptide" comprises peptides that inhibit or down-regulate activation of the IL-1 receptor by IL-1. IL-1 receptor activation results from formation of a complex among IL-1, IL-1 receptor, and IL-1 receptor accessory protein. IL-1 antagonist or IL-1ra-mimetic peptides bind to IL-1, IL-1 receptor, or IL-1 receptor accessory protein and obstruct complex formation among any two or three components of the complex. Exemplary IL-1 antagonist or IL-1ra-mimetic peptides can be identified or derived as described in U.S. Pat. Nos. 5,608,035, 5,786,331, 5,880,096, or any of the references in Table 2 identified as having IL-1ra-mimetic or IL-1 antagonistic subject matter. Those of ordinary skill in the art appreciate that each of these references enables one to select different peptides than actually disclosed therein by following the disclosed procedures with different peptide libraries.

The term "VEGF-antagonist peptide" comprises peptides that can be identified or derived as described in Fairbrother (1998), <u>Biochem.</u> 37:

17754-64, and in any of the references in Table 2 identified as having VEGF-antagonistic subject matter. Those of ordinary skill in the art appreciate that each of these references enables one to select different peptides than actually disclosed therein by following the disclosed procedures with different peptide libraries.

The term "MMP inhibitor peptide" comprises peptides that can be identified or derived as described in Koivunen (1999), Nature Biotech. 17: 768-74 and in any of the references in Table 2 identified as having MMP inhibitory subject matter. Those of ordinary skill in the art appreciate that each of these references enables one to select different peptides than actually disclosed therein by following the disclosed procedures with different peptide libraries.

Additionally, physiologically acceptable salts of the compounds of this invention are also encompassed herein. By "physiologically acceptable salts" is meant any salts that are known or later discovered to be pharmaceutically acceptable. Some specific examples are: acetate; trifluoroacetate; hydrohalides, such as hydrochloride and hydrobromide; sulfate; citrate; tartrate; glycolate; and oxalate.

Structure of compounds

<u>In General</u>. In the compositions of matter prepared in accordance with this invention, the peptide may be attached to the vehicle through the peptide's N-terminus or C-terminus. Thus, the vehicle-peptide molecules of this invention may be described by the following formula I:

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$$(X^{1})_{a}-F^{1}-(X^{2})_{b}$$

wherein:

F¹ is a vehicle (preferably an Fc domain);

 $X^{1} \text{ and } X^{2} \text{ are each independently selected from -(L^{1})}_{c} - P^{1}, -(L^{1})_{c} - P^{1} - (L^{2})_{d} - P^{2}, -(L^{1})_{c} - P^{1} - (L^{2})_{d} - P^{2} - (L^{3})_{e} - P^{3} - (L^{4})_{f} - P^{4}$

P¹, P², P³, and P⁴ are each independently sequences of pharmacologically active peptides;

L¹, L², L³, and L⁴ are each independently linkers; and a, b, c, d, e, and f are each independently 0 or 1, provided that at least one of a and b is 1.

Thus, compound I comprises preferred compounds of the formulae

$$X^1-F^1$$

and multimers thereof wherein F^1 is an Fc domain and is attached at the C-terminus of X^1 ;

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and multimers thereof wherein F^1 is an Fc domain and is attached at the N-terminus of X^2 ;

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and multimers thereof wherein F^1 is an Fc domain and is attached at the N-terminus of -(L^1)_c- P^1 ; and

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$$F^{1}-(L^{1})_{c}-P^{1}-(L^{2})_{d}-P^{2}$$

and multimers thereof wherein F^1 is an Fc domain and is attached at the N-terminus of $-L^1-P^1-L^2-P^2$.

<u>Peptides</u>. Any number of peptides may be used in conjunction with the present invention. Of particular interest are peptides that mimic the activity of EPO, TPO, growth hormone, G-CSF, GM-CSF, IL-1ra, leptin, CTLA4, TRAIL, TGF- α , and TGF- β . Peptide antagonists are also of interest, particularly those antagonistic to the activity of TNF, leptin, any of the interleukins (IL-1, 2, 3, ...), and proteins involved in complement activation (e.g., C3b). Targeting peptides are also of interest, including

tumor-homing peptides, membrane-transporting peptides, and the like.

All of these classes of peptides may be discovered by methods described in the references cited in this specification and other references.

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Phage display, in particular, is useful in generating peptides for use in the present invention. It has been stated that affinity selection from libraries of random peptides can be used to identify peptide ligands for any site of any gene product. Dedman et al. (1993), J. Biol. Chem. 268: 23025-30. Phage display is particularly well suited for identifying peptides that bind to such proteins of interest as cell surface receptors or any proteins having linear epitopes. Wilson et al. (1998), Can. J. Microbiol. 44: 313-29; Kay et al. (1998), Drug Disc. Today 3: 370-8. Such proteins are extensively reviewed in Herz et al. (1997), J. Receptor & Signal Transduction Res. 17(5): 671-776, which is hereby incorporated by reference. Such proteins of interest are preferred for use in this invention.

A particularly preferred group of peptides are those that bind to cytokine receptors. Cytokines have recently been classified according to their receptor code. See Inglot (1997), <u>Archivum Immunologiae et Therapiae Experimentalis</u> 45: 353-7, which is hereby incorporated by reference. Among these receptors, most preferred are the CKRs (family I in Table 3). The receptor classification appears in Table 3.

PCT/US99/25044

Table 3—Cytokine Receptors Classified by Receptor Code

Cytokines	s (ligands)	Recept	or Type
family	subfamily	family	subfamily
Hematopoietic cytokines	1. IL-2, IL-4, IL-7, IL-9, IL-13, IL- 15	I. Cytokine R (CKR)	1. shared γCr
	2. IL-3, IL-5, GM- CSF		2. shared GP 140 βR
	3. IL-6, IL-11, IL- 12, LIF, OSM, CNTF, leptin (OB)		3. 3.shared RP 130
	4. G-CSF, EPO, TPO, PRL, GH		4. "single chain" R
	5. IL-17, HVS-IL-		5. other R°
II. IL-10 ligands	IL-10, BCRF-1, HSV-IL-10	II. IL-10 R	
III. Interferons	 IFN-αl, α2, α4, m, t, IFN-β^d 	III. Interferon R	1. IFNAR
	2. IFN-γ		2. IFNGR
IV. IL-1 ligands	1. IL-1α, IL-1β, iL- 1Ra	IV. IL-1R	
V. TNF ligands	1. TNF-α, TNF-β (LT), FAS1, CD40 L, CD30L, CD27 L	V. NGF/TNF R ^a	
VI. Chemokines	1. α chemokines: IL-8, GRO α, β, γ, IF-10, PF-4, SDF-1	VI. Chemokine R	1. CXCR
	2. β chemokines: MiP1α, MIP1β, MCP-1,2,3,4, RANTES, eotaxin		2. CCR
	 γ chemokines: lymphotactin 		 3. CR 4. DARC'

° TNF receptors use multiple, distinct intracellular molecules for signal transduction including "death domain" of FAS R and 55 kDa TNF-αR that participates in their cytotoxic effects. NGF/TNF R can bind both NGF and related factors as well as TNF ligands. Chemokine receptors are G protein-coupled, seven transmembrane (7TM, serpentine) domain receptors.

The Duffy blood group antigen (DARC) is an erythrocyte receptor that can bind several different chemokines. It belongs to the immunoglobulin superfamily but characteristics of its signal transduction events remain unclear.

^c IL-17R belongs to the CKR family but is not assigned to any of the 4 indicated subjamilies.
^d Other IFN type I subtypes remain unassigned. Hematopoietic cytokines, IL-10 ligands and interferons do not possess functional intrinsic protein kinases. The signaling molecules for the cytokines are JAK's, STATs and related non-receptor molecules. IL-14, IL-16 and IL-18 have been cloned but according to the receptor code they remain unassigned.

VII. Growth factors		VII. RKF	1.	TK sub-family
	1.1 SCF, M-CSF,		1.1	lgTK III R
	PDGF-AA, AB,			
	BB, FLT-3L,			
	VEGF, SSV-			
	PDGF		10	IgTK IV R
	1.2 FGFα, FGFβ			
	1.3 EGF, TGF-α,	ŀ	1.3	Cysteine-rich
	VV-F19 (EGF-	1		TK-I
	like)	}		
	1.4 IGF-I, IGF-II,		1.4	Cysteine rich
	Insulin			TK-II
	1.5 NGF, BDNF,		1.5	Cysteine knot
	NT-3, NT-4°			TK V
	2. TGF-β1,β2,β3]	2.	STK subfamily ^h

Exemplary peptides for this invention appear in Tables 4 through 20 below. These peptides may be prepared by methods disclosed in the art. Single letter amino acid abbreviations are used. The X in these sequences (and throughout this specification, unless specified otherwise in a particular instance) means that any of the 20 naturally occurring amino acid residues may be present. Any of these peptides may be linked in tandem (i.e., sequentially), with or without linkers, and a few tandemlinked examples are provided in the table. Linkers are listed as "A" and may be any of the linkers described herein. Tandem repeats and linkers are shown separated by dashes for clarity. Any peptide containing a cysteinyl residue may be cross-linked with another Cys-containing peptide, either or both of which may be linked to a vehicle. A few crosslinked examples are provided in the table. Any peptide having more than one Cys residue may form an intrapeptide disulfide bond, as well; see, for example, EPO-mimetic peptides in Table 5. A few examples of intrapeptide disulfide-bonded peptides are specified in the table. Any of these peptides may be derivatized as described herein, and a few derivatized examples are provided in the table. Derivatized peptides in

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⁹ The neurotrophic cytokines can associate with NGF/TNF receptors also.

the tables are exemplary rather than limiting, as the associated underivatized peptides may be employed in this invention, as well. For derivatives in which the carboxyl terminus may be capped with an amino group, the capping amino group is shown as -NH₂. For derivatives in which amino acid residues are substituted by moieties other than amino acid residues, the substitutions are denoted by σ , which signifies any of the moieties described in Bhatnagar et al. (1996), J. Med. Chem. 39: 3814-9 and Cuthbertson et al. (1997), J. Med. Chem. 40: 2876-82, which are incorporated by reference. The J substituent and the Z substituents (Z_s, Z_s) $...Z_{40}$) are as defined in U.S. Pat. Nos. 5,608,035 ,5,786,331, and 5,880,096, which are incorporated by reference. For the EPO-mimetic sequences (Table 5), the substituents X, through X_{ij} and the integer "n" are as defined in WO 96/40772, which is incorporated by reference. The substituents "Y," "O," and "+" are as defined in Sparks et al. (1996), Proc. Natl. Acad. Sci. 93: 1540-4, which is hereby incorporated by reference. X_4 , X_5 , X_6 , and X_7 are as defined in U.S. Pat. No. 5,773,569, which is hereby incorporated by reference, except that: for integrin-binding peptides, X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , and X_8 are as defined in International applications WO 95/14714, published June 1, 1995 and WO 97/08203, published March 6, 1997, which are also incorporated by reference; and for VIP-mimetic peptides, X₁, X₁', X_1 , X_2 , X_3 , X_4 , X_5 , X_6 and X_1 and the integers m and n are as defined in WO 97/40070, published October 30, 1997, which is also incorporated by reference. Xaa and Yaa below are as defined in WO 98/09985, published March 12, 1998, which is incorporated by reference. AA, AA, AB, AB, and AC are as defined in International application WO 98/53842, published December 3, 1998, which is incorporated by reference. X^1 , X^2 , X^3 , and X⁴ in Table 17 only are as defined in European application EP 0 911

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^h STKS may encompass many other TGF-β-related factors that remain unassigned. The protein kinases are intrinsic part of the intracellular domain of receptor kinase family (RKF). The enzymes participate in the signals transmission via the receptors.

393, published April 28, 1999. Residues appearing in boldface are D-amino acids. All peptides are linked through peptide bonds unless otherwise noted. Abbreviations are listed at the end of this specification. In the "SEQ ID NO." column, "NR" means that no sequence listing is required for the given sequence.

Table 4—IL-1 antagonist peptide sequences

Sequence/structure	SEQ
	ID NO:
$Z_{11}Z_7Z_8QZ_5YZ_6Z_3Z_{10}$	212
XXQZ,YZ,XX	907
Z,XQZ,YZ,XX	908
Z,Z,QZ,YZ,Z,Z, ₁₀	909
$Z_{1}Z_{2}Z_{3}QZ_{5}YZ_{5}Z_{5}Z_{10}$	910
$Z_{12}Z_{13}Z_{14}Z_{15}Z_{16}Z_{17}Z_{18}Z_{19}Z_{20}Z_{21}Z_{22}Z_{11}Z_{7}Z_{8}QZ_{5}YZ_{6}Z_{9}Z_{10}L$	917
$Z_{23}NZ_{24}Z_{32}Z_{25}Z_{26}Z_{27}Z_{26}Z_{26}Z_{30}Z_{40}$	979
TANVSSFEWTPYYWQPYALPL	213
SWTDYGYWQPYALPISGL	214
ETPFTWEESNAYYWQPYALPL	215
ENTYSPNWADSMYWQPYALPL	216
SVGEDHNFWTSEYWQPYALPL	217
DGYDRWRQSGERYWQPYALPL	218
FEWTPGYWQPY	219
FEWTPGYWQHY	220
FEWTPGWYQJY	221
AcFEWTPGWYQJY	222
FEWTPGWpYQJY	223
FAWTPGYWQJY	224
FEWAPGYWQJY	225
FEWVPGYWQJY	226
FEWTPGYWQJY	227
AcFEWTPGYWQJY	228
FEWTPaWYQJY	229
FEWTPSarWYQJY	230
FEWTPGYYQPY	231
FEWTPGWWQPY	232
FEWTPNYWQPY	233
FEWTPvYWQJY	234
FEWTPecGYWQJY	235
FEWTPAIbYWQJY	236
FEWTSarGYWQJY	237
FEWTPGYWQPY	238
FEWTPGYWQHY	239
FEWTPGWYQJY	240

FEWTPGW-PY-QJY 242 FAWTPGYWQJY 243 FEWAPGYWQJY 244 FEWTPGYWQJY 245 FEWTPGYWQJY 246 AcFEWTPGYWQJY 246 AcFEWTPGYWQJY 247 FEWTPGYWQJY 247 FEWTPGYWQJY 248 FEWTPSARWYQJY 248 FEWTPSARWYQJY 259 FEWTPGYYQPY 250 FEWTPGYYQPY 251 FEWTPGYYQPY 251 FEWTPGWWQPY 251 FEWTPGWWQPY 252 FEWTPLYWQJY 253 FEWTPcGYWQJY 254 FEWTPAIbYWQJY 255 FEWTPAIbYWQJY 255 FEWTSARGYWQJY 256 FEWTPGYYQJY 256 FEWTPGYYQJY 256 FEWTPGYYQJY 257 TINAPEWTPGYYQJY 259 FEWTPGYYQJY 260 FEWTPSYYQJY 260 FEWTPSYYQJY 260 FEWTPSYYQJY 261 FEWTPNYQJY 262 TKPR 263 RKSSK 264 RKQDKR 265 NRKQDK 266 NRKQDKR 267 ENRKQDKR 267 ENRKQDKR 267 TLVYWQPYSUQT 671 RGDYWQPYSUQT 675 SRVWFQPYSUQT 675 SRVWGPYSUQT 675 SRVWGPYSUQR 681 LVYWQPYSUQR 681 FLVYWQPYSUQR 681 FLVYWQPYSUQR 681 FLVYWQPYSUQR 682 SLYWQPYSUQR 683 SLYWQPYSUQR 684 TRLYWQPYSUQR 687 KIVYWQPYSUQR 687 KIVYWQPYSUQR 687 KIVYWQPYSUQR 688 KIVYWQPYSUQR 687 KIVYWQPYSUQR 687 KIVYWQPYSUQR 687 KIVYWQPYSUQR 687 KIVYWQPYSUQR 687 KIVYWQPYSUQR 688		
FAWTPGYWQJY	AcFEWTPGWYQJY	241
FEWAPGYWQJY 244 FEWTPGYWQJY 245 FEWTPGYWQJY 246 AcFEWTPGYWQJY 247 FEWTPAWYQJY 248 FEWTPSarWYQJY 249 FEWTPSarWYQJY 250 FEWTPGWWQPY 251 FEWTPGWWQPY 252 FEWTPNYWQJY 253 FEWTPGGYWQJY 254 FEWTPAIbYWQJY 255 FEWTPAIBYWQJY 256 FEWTPGYWQPYALPL 257 INApEWTPGYYQJY 258 YEWTPGYYQJY 259 FEWTPGYYQJY 260 FEWTPSYYQJY 261 FEWTPSYYQJY 262 TKPR 263 RKSSK 264 RKQDK 265 NRKQDK 265 NRKQDK 266 RKQDKR 267 ENPKQDKRF 268 VTKFYF 270 VTKFY 271 SHLYWQPYSUQT 673 TLVYWQPYSUQT 675	FEWTPGW-pY-QJY	
FEWVPGYWQJY 245 FEWTPGYWQJY 246 AcFEWTPGYWQJY 247 FEWTPAWYQJY 248 FEWTPSarWYQJY 249 FEWTPSarWYQDY 250 FEWTPGYWQPY 251 FEWTPGWWQPY 251 FEWTPYWQJY 253 FEWTPecGYWQJY 254 FEWTPAibYWQJY 255 FEWTSarGYWQJY 256 FEWTPGYYQJY 256 FEWTPGYYQJY 257 INApEWTPGYYQJY 259 FEWTPGYYQJY 260 FEWTPSYYQJY 261 FEWTPSYYQJY 261 FEWTPNYYQJY 262 TKPR 263 RKSSK 264 RKODK 265 NRKQDK 265 NRKQDK 266 RKQDKR 266 RKQDKR 266 RKQDKR 266 VTKFY 270 VTDFY 271 SHLYWQPYSVQT 673		
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FEWTPGWWQPY 251 FEWTPNYWQPY 252 FEWTPVYWQJY 253 FEWTPecGYWQJY 255 FEWTPAibYWQJY 256 FEWTPGYWQPYALPL 257 1NapEWTPGYYQJY 258 YEWTPGYYQJY 259 FEWYPGYYQJY 261 FEWTPNYYQJY 261 FEWTPNYYQJY 262 TKPR 263 RKSSK 264 RKQDK 265 NRKQDK 266 RKQDK 266 NRKQDK 266 RKQDKRF 269 VTKFY 270 VTLYFY 271 SHLYWQPYSVQ 671 TLVYWQPYSVQT 672 RGDYWQPYSVQT 675 SRVWFQPYSLQS 676 NMVYWQPYSVQT 678 TFVYWQPYSVQT 679 TLVYWQPYSVQR 681 SPVFWQPYSLQM 681 SPVFWQPYSLQM 684 TRLYWQPYSVQR 685	FEWTPSarWYQJY	249
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FEWTPAIBYWQJY 255 FEWTSarGYWQJY 256 FEWTPGYWQPYALPL 257 1NapEWTPGYYQJY 258 YEWPGYYQJY 259 FEWTPSYYQJY 260 FEWTPNYYQJY 261 FEWTPNYYQJY 262 TKPR 263 RKSSK 264 RKQDK 265 NRKQDK 266 RKQDKR 267 ENRKQDKRF 268 VTKFY 270 VTDFY 271 SHLYWQPYSVQ 671 TLVYWQPYSLQT 672 RGDYWQPYSVQS 673 VHVYWQPYSVQT 674 RLVYWQPYSVQT 676 NMVYWQPYSVQT 678 TFVYWQPYSLQR 681 SPVFWQPYSLQR 681 SPVFWQPYSLQR 681 SPVFWQPYSLQR 685 RLYYWQPYSLQR 685 RCDYWQPYSLQR 685 RCDYWQPYSLQR 685 KIVYWQPYSLQR 685	FEWTPVYWQJY	253
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YEWTPGYYQJY 259 FEWVPGYYQJY 260 FEWTPSYYQJY 261 FEWTPNYYQJY 262 TKPR 263 RKSSK 264 RKQDK 265 NRKQDK 266 RKQDKR 267 ENRKQDKRF 268 VTKFYF 269 VTKFY 270 VTDFY 271 SHLYWQPYSVQ 671 TLVYWQPYSLQT 672 RGDYWQPYSVQS 673 VHVYWQPYSVQT 674 RLVYWQPYSVQT 675 SRVWFQPYSLQS 676 NMVYWQPYSQT 678 TEVYWQPYSLQT 678 TEVYWQPYSLQR 680 RLVYWQPYSLQR 681 SPVFWQPYSLQR 681 SPVFWQPYSLQM 684 TRLYWQPYSVQR 685 RCDYWQPYSVQT 686 MRVFWQPYSVQN 687 KIVYWQPYSVQT 688	FEWTPGYWQPYALPL	257
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FEWTPNYYQJY 262 TKPR 263 RKSSK 264 RKQDK 265 NRKQDK 266 RKQDKR 267 ENRKQDKRF 268 VTKFYF 269 VTKFY 270 VTDFY 271 SHLYWQPYSVQ 671 TLVYWQPYSLQT 672 RGDYWQPYSVQS 673 VHVYWQPYSVQT 674 RLVYWQPYSVQT 675 SRVWFQPYSLQS 676 NMVYWQPYSIQT 678 TFVYWQPYSIQT 678 TFVYWQPYSIQR 680 RLVYWQPYSIQR 681 SPVFWQPYSIQI 682 WIEWWQPYSVQR 683 SLIYWQPYSUQM 684 TRLYWQPYSVQT 686 MRVFWQPYSVQT 686 MRVFWQPYSVQT 686 MRVFWQPYSVQT 687 KIVYWQPYSVQT 688	FEWVPGYYQJY	260
TKPR 263 RKSSK 264 RKQDK 265 NRKQDKR 266 RKQDKR 267 ENRKQDKRF 268 VTKFYF 269 VTKFY 270 VTDFY 271 SHLYWQPYSVQ 671 TLVYWQPYSLQT 672 RGDYWQPYSVQS 673 VHVYWQPYSVQT 674 RLVYWQPYSVQT 675 SRVWFQPYSLQS 676 NMVYWQPYSIQT 677 SVVFWQPYSVQT 678 TFVYWQPYSLQR 680 RLVYWQPYSIQR 681 SPVFWQPYSIQI 682 WIEWWQPYSIQR 683 SLIYWQPYSLQM 684 TRLYWQPYSVQR 685 RCDYWQPYSVQN 686 MRVFWQPYSVQN 687 KIVYWQPYSVQT 688	FEWTPSYYQJY	
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RKQDK 265 NRKQDK 266 RKQDKR 267 ENRKQDKRF 268 VTKFYF 269 VTKFY 270 VTDFY 271 SHLYWQPYSVQ 671 TLVYWQPYSLQT 672 RGDYWQPYSVQS 673 VHVYWQPYSVQT 674 RLVYWQPYSVQT 675 SRVWFQPYSLQS 676 NMVYWQPYSLQT 677 SVVFWQPYSVQT 678 TFVYWQPYSLQR 680 RLVYWQPYSVQR 681 SPVFWQPYSLQN 681 SPVFWQPYSLQN 683 SLIYWQPYSLQM 684 TRLYWQPYSVQR 685 RCDYWQPYSVQT 686 MRVFWQPYSVQT 686 MRVFWQPYSVQT 687 KIVYWQPYSVQT 688	TKPR	
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RKQDKR 267 ENRKQDKRF 268 VTKFYF 269 VTKFY 270 VTDFY 271 SHLYWQPYSVQ 671 TLVYWQPYSLQT 672 RGDYWQPYSVQS 673 VHVYWQPYSVQT 674 RLVYWQPYSVQT 675 SRVWFQPYSLQS 676 NMVYWQPYSLQT 678 TFVYWQPYSVQT 678 TFVYWQPYSLQR 680 RLVYWQPYSVQR 681 SPVFWQPYSIQI 682 WIEWWQPYSVQS 683 SLIYWQPYSLQM 684 TRLYWQPYSVQR 685 RCDYWQPYSVQT 686 MRVFWQPYSVQN 687 KIVYWQPYSVQT 688	RKQDK	265
ENRKQDKRF 268 VTKFYF 269 VTKFY 270 VTDFY 271 SHLYWQPYSVQ 671 TLVYWQPYSLQT 672 RGDYWQPYSVQS 673 VHVYWQPYSVQT 674 RLVYWQPYSVQT 675 SRVWFQPYSLQS 676 NMVYWQPYSIQT 677 SVVFWQPYSVQT 678 TFVYWQPYSIQR 680 RLVYWQPYSIQR 681 SPVFWQPYSIQI 682 WIEWWQPYSVQS 683 SLIYWQPYSLQM 684 TRLYWQPYSVQR 685 RCDYWQPYSVQT 686 MRVFWQPYSVQN 687 KIVYWQPYSVQT 688	NRKQDK	266
VTKFYF 269 VTKFY 270 VTDFY 271 SHLYWQPYSVQ 671 TLVYWQPYSLQT 672 RGDYWQPYSVQS 673 VHVYWQPYSVQT 674 RLVYWQPYSVQT 675 SRVWFQPYSLQS 676 NMVYWQPYSIQT 677 SVVFWQPYSIQT 678 TFVYWQPYSIQR 680 RLVYWQPYSIQR 681 SPVFWQPYSIQI 682 WIEWWQPYSVQR 683 SLIYWQPYSIQM 684 TRLYWQPYSVQR 685 RCDYWQPYSVQR 685 MRVFWQPYSVQN 687 KIVYWQPYSVQT 688		·
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MNDQTSEVSTFP YWQPYALPL SWSEAFEQPRNL YWQPYALPL QYAEPSALNDWG YWQPYALPL R65 NGDWATADWSNY YWQPYALPL R66 THDEHI YWQPYALPL R67 MLEKTYTTWTPG YWQPYALPL R68 WSDPLTRDADL YWQPYALPL R70 GDDAAWRTDSLT YWQPYALPL R71 AIIRQLYRWSEM YWQPYALPL ENTYSPNWADSM YWQPYALPL S72 ENTYSPNWADSM YWQPYALPL S73 MNDQTSEVSTFP YWQPYALPL S75 QTPFTWEESNAY YWQPYALPL R76 ENPFTWQESNAY YWQPYALPL R77 VTPFTWEDSNVF YWQPYALPL R78 QIPFTWEGSNAY YWQPYALPL R79 QAPLTWQESAAY YWQPYALPL EPTFTWEESNAY YWQPYALPL R80 EPTFTWEESNAY YWQPYALPL R81 TTLTWEESNAY YWQPYALPL R82 ESPLTWEESNAY YWQPYALPL R83 ETPLTWEESNAY YWQPYALPL R84 ETPLTWEESNAY YWQPYALPL R85 ETPLTWEESNAY YWQPYALPL R86 S87 ETPLTWEESNAY YWQPYALPL R87 R88 ETPLTWEESNAY YWQPYALPL R88 ETPLTWEESNAY YWQPYALPL R88 ETPLTWEESNAY YWQPYALPL R88 S87 ETPTWEESNAY YWQPYALPL R88 S87 ETPFTWEESNAY YWQPYALPL R87 ETPFTWEESNAY YWQPYALPL R88 ETPLTWEESNAY YWQPYALPL R88 S87 ETPFTWEESNAY YWQPYALPL R88 ETPLTWEESNAY YWQPYALPL R88 S87 ETPFTWEESNAY YWQPYALPL R88 S87		
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QYAEPSALNDWG YWQPYALPL NGDWATADWSNY YWQPYALPL 866 THDEHI YWQPYALPL MLEKTYTTWTPG YWQPYALPL 868 WSDPLTRDADL YWQPYALPL SDAFTTQDSQAM YWQPYALPL GDDAAWRTDSLT YWQPYALPL AIIRQLYRWSEM YWQPYALPL ENTYSPNWADSM YWQPYALPL SVGEDHNFWTSE YWQPYALPL SVGEDHNFWTSE YWQPYALPL ENPFTWEESNAY YWQPYALPL ENPFTWQESNAY YWQPYALPL S77 VTPFTWEDSNVF YWQPYALPL B78 QIPFTWEQSNAY YWQPYALPL B79 QAPLTWQESAAY YWQPYALPL B80 EPTFTWEESKAT YWQPYALPL B81 TTTLTWEESNAY YWQPYALPL B82 ESPLTWEESSAL YWQPYALPL B83 ETPLTWEESNAY YWQPYALPL B84 ETPLTWEESNAY YWQPYALPL B85 EALFTWKESTAY YWQPYALPL B86 STP-TWEESNAY YWQPYALPL B87 ETPLTWEESNAY YWQPYALPL B86 STP-TWEESNAY YWQPYALPL B87 ETPLTWEESNAY YWQPYALPL B86 STP-TWEESNAY YWQPYALPL B87 ETPLTWEESNAY YWQPYALPL B87 ETPLTWEESNAY YWQPYALPL B87 ETPLTWEESNAY YWQPYALPL B87	MNDQTSEVSTFP YWQPYALPL	863
NGDWATADWSNY YWQPYALPL THDEHI YWQPYALPL MLEKTYTTWTPG YWQPYALPL S68 WSDPLTRDADL YWQPYALPL S09 SDAFTTQDSQAM YWQPYALPL GDDAAWRTDSLT YWQPYALPL AIIRQLYRWSEM YWQPYALPL ENTYSPNWADSM YWQPYALPL S72 ENTYSPNWADSM YWQPYALPL S73 MNDQTSEVSTFP YWQPYALPL S75 QTPFTWEESNAY YWQPYALPL ENPFTWQESNAY YWQPYALPL S76 ENPFTWQESNAY YWQPYALPL S77 VTPFTWEDSNVF YWQPYALPL S78 QIPFTWEQSNAY YWQPYALPL S79 QAPLTWQESAAY YWQPYALPL S80 EPTFTWEESKAT YWQPYALPL S81 TTTLTWEESNAY YWQPYALPL S82 ESPLTWEESSAL YWQPYALPL S83 ETPLTWEESNAY YWQPYALPL S84 EAFTWAESNAY YWQPYALPL S85 EALFTWKESTAY YWQPYALPL S86 STP-TWEESNAY YWQPYALPL S87 ETPFTWEESNAY YWQPYALPL S87 ETPFTWEESNAY YWQPYALPL S86 STP-TWEESNAY YWQPYALPL S87 ETPFTWEESNAY YWQPYALPL S87	SWSEAFEQPRNL YWQPYALPL	864
THDEHI YWQPYALPL MLEKTYTTWTPG YWQPYALPL WSDPLTRDADL YWQPYALPL SDAFTTQDSQAM YWQPYALPL GDDAAWRTDSLT YWQPYALPL AIIRQLYRWSEM YWQPYALPL ENTYSPNWADSM YWQPYALPL 873 MNDQTSEVSTFP YWQPYALPL 875 QTPFTWEESNAY YWQPYALPL ENPFTWQESNAY YWQPYALPL 876 ENPFTWQESNAY YWQPYALPL 877 VTPFTWEDSNVF YWQPYALPL 878 QIPFTWEQSNAY YWQPYALPL 879 QAPLTWQESAAY YWQPYALPL 881 TTTLTWEESNAY YWQPYALPL 882 ESPLTWEESSAL YWQPYALPL 883 ETPLTWEESNAY YWQPYALPL 884 EATFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 887	QYAEPSALNDWG YWQPYALPL	865
MLEKTYTTWTPG YWQPYALPL WSDPLTRDADL YWQPYALPL SDAFTTQDSQAM YWQPYALPL GDDAAWRTDSLT YWQPYALPL AIIRQLYRWSEM YWQPYALPL ENTYSPNWADSM YWQPYALPL SVGEDHNFWTSE YWQPYALPL SVGEDHNFWTSE YWQPYALPL SVGEDHNFWTSE YWQPYALPL ENPFTWQESNAY YWQPYALPL S75 QTPFTWEESNAY YWQPYALPL 876 ENPFTWQESNAY YWQPYALPL 877 VTPFTWEDSNVF YWQPYALPL S79 QAPLTWQESAAY YWQPYALPL EPTFTWEESKAT YWQPYALPL 880 EPTFTWEESKAT YWQPYALPL 881 TTTLTWEESNAY YWQPYALPL 882 ESPLTWEESSAL YWQPYALPL 883 ETPLTWEESNAY YWQPYALPL 884 ETPLTWEESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 887	NGDWATADWSNY YWQPYALPL	866
WSDPLTRDADL YWQPYALPL SDAFTTQDSQAM YWQPYALPL B70 GDDAAWRTDSLT YWQPYALPL AIIRQLYRWSEM YWQPYALPL ENTYSPNWADSM YWQPYALPL ENTYSPNWADSM YWQPYALPL B73 MNDQTSEVSTFP YWQPYALPL SVGEDHNFWTSE YWQPYALPL SVGEDHNFWTSE YWQPYALPL B75 QTPFTWEESNAY YWQPYALPL B76 ENPFTWQESNAY YWQPYALPL B77 VTPFTWEDSNVF YWQPYALPL B78 QIPFTWEQSNAY YWQPYALPL B79 QAPLTWQESAAY YWQPYALPL B80 EPTFTWEESKAT YWQPYALPL B81 TTTLTWEESNAY YWQPYALPL B82 ESPLTWEESNAY YWQPYALPL B83 ETPLTWEESNAY YWQPYALPL B84 EATFTWAESNAY YWQPYALPL B85 EALFTWKESTAY YWQPYALPL B86 STP-TWEESNAY YWQPYALPL B87 ETPFTWEESNAY YWQPYALPL B87 ETPFTWEESNAY YWQPYALPL B87	THDEHI YWQPYALPL	867
SDAFTTQDSQAM YWQPYALPL GDDAAWRTDSLT YWQPYALPL AIIRQLYRWSEM YWQPYALPL ENTYSPNWADSM YWQPYALPL ENTYSPNWADSM YWQPYALPL ENTYSPNWADSM YWQPYALPL SVGEDHNFWTSE YWQPYALPL SVGEDHNFWTSE YWQPYALPL SVGEDHNFWTSE YWQPYALPL ENPFTWQESNAY YWQPYALPL S75 QTPFTWEESNAY YWQPYALPL 876 ENPFTWQESNAY YWQPYALPL 877 VTPFTWEDSNVF YWQPYALPL 879 QAPLTWQESAAY YWQPYALPL 880 EPTFTWEESKAT YWQPYALPL 881 TTTLTWEESNAY YWQPYALPL 882 ESPLTWEESSAL YWQPYALPL 883 ETPLTWEESNAY YWQPYALPL 884 EAFFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 887	MLEKTYTTWTPG YWQPYALPL	868
GDDAAWRTDSLT YWQPYALPL AIIRQLYRWSEM YWQPYALPL ENTYSPNWADSM YWQPYALPL ENTYSPNWADSM YWQPYALPL ENTYSPNWADSM YWQPYALPL SVGEDHNFWTSE YWQPYALPL SVGEDHNFWTSE YWQPYALPL B75 QTPFTWEESNAY YWQPYALPL ENPFTWQESNAY YWQPYALPL S76 ENPFTWQESNAY YWQPYALPL B77 VTPFTWEDSNVF YWQPYALPL B78 QIPFTWEQSNAY YWQPYALPL B79 QAPLTWQESAAY YWQPYALPL B80 EPTFTWEESKAT YWQPYALPL B81 TTTLTWEESNAY YWQPYALPL B82 ESPLTWEESNAY YWQPYALPL B83 ETPLTWEESNAY YWQPYALPL B84 EAFFTWAESNAY YWQPYALPL B85 EALFTWKESTAY YWQPYALPL B86 STP-TWEESNAY YWQPYALPL B87 ETPFTWEESNAY YWQPYALPL B87	WSDPLTRDADL YWQPYALPL	869
AIIRQLYRWSEM YWQPYALPL ENTYSPNWADSM YWQPYALPL ENTYSPNWADSM YWQPYALPL 873 MNDQTSEVSTFP YWQPYALPL SVGEDHNFWTSE YWQPYALPL 875 QTPFTWEESNAY YWQPYALPL ENPFTWQESNAY YWQPYALPL 877 VTPFTWEDSNVF YWQPYALPL 878 QIPFTWEQSNAY YWQPYALPL 879 QAPLTWQESAAY YWQPYALPL 880 EPTFTWEESKAT YWQPYALPL 881 TTTLTWEESNAY YWQPYALPL 882 ESPLTWEESNAY YWQPYALPL 883 ETPLTWEESNAY YWQPYALPL 884 EAFFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 887	SDAFTTQDSQAM YWQPYALPL	870
ENTYSPNWADSM YWQPYALPL MNDQTSEVSTFP YWQPYALPL SVGEDHNFWTSE YWQPYALPL QTPFTWEESNAY YWQPYALPL ENPFTWQESNAY YWQPYALPL VTPFTWEDSNVF YWQPYALPL QIPFTWEQSNAY YWQPYALPL QAPLTWQESAAY YWQPYALPL EPTFTWEESKAT YWQPYALPL 880 EPTFTWEESKAT YWQPYALPL 881 TTTLTWEESNAY YWQPYALPL 882 ESPLTWEESSAL YWQPYALPL 883 ETPLTWEESNAY YWQPYALPL 884 EATFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 887	GDDAAWRTDSLT YWQPYALPL	871
MNDQTSEVSTFP YWQPYALPL SVGEDHNFWTSE YWQPYALPL QTPFTWEESNAY YWQPYALPL ENPFTWQESNAY YWQPYALPL 876 ENPFTWQESNAY YWQPYALPL 877 VTPFTWEDSNVF YWQPYALPL 878 QIPFTWEQSNAY YWQPYALPL 880 EPTFTWEESKAT YWQPYALPL 881 TTTLTWEESNAY YWQPYALPL 882 ESPLTWEESSAL YWQPYALPL 883 ETPLTWEESNAY YWQPYALPL 884 EATFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 887	AIIRQLYRWSEM YWQPYALPL	872
SVGEDHNFWTSE YWQPYALPL QTPFTWEESNAY YWQPYALPL ENPFTWQESNAY YWQPYALPL VTPFTWEDSNVF YWQPYALPL QIPFTWEQSNAY YWQPYALPL QAPLTWQESAAY YWQPYALPL EPTFTWEESKAT YWQPYALPL ESPLTWEESNAY YWQPYALPL ESPLTWEESSAL YWQPYALPL ESPLTWEESSAL YWQPYALPL EATFTWAESNAY YWQPYALPL EATFTWAESNAY YWQPYALPL EALFTWKESTAY YWQPYALPL S86 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 888	ENTYSPNWADSM YWQPYALPL	873
QTPFTWEESNAY YWQPYALPL 876 ENPFTWQESNAY YWQPYALPL 877 VTPFTWEDSNVF YWQPYALPL 878 QIPFTWEQSNAY YWQPYALPL 879 QAPLTWQESAAY YWQPYALPL 880 EPTFTWEESKAT YWQPYALPL 881 TTTLTWEESNAY YWQPYALPL 882 ESPLTWEESSAL YWQPYALPL 883 ETPLTWEESNAY YWQPYALPL 884 EATFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 887	MNDQTSEVSTFP YWQPYALPL	874
ENPFTWQESNAY YWQPYALPL 877 VTPFTWEDSNVF YWQPYALPL 878 QIPFTWEQSNAY YWQPYALPL 879 QAPLTWQESAAY YWQPYALPL 880 EPTFTWEESKAT YWQPYALPL 881 TTTLTWEESNAY YWQPYALPL 882 ESPLTWEESSAL YWQPYALPL 883 ETPLTWEESNAY YWQPYALPL 884 EATFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 888	SVGEDHNFWTSE YWQPYALPL	875
VTPFTWEDSNVF YWQPYALPL 878 QIPFTWEQSNAY YWQPYALPL 879 QAPLTWQESAAY YWQPYALPL 880 EPTFTWEESKAT YWQPYALPL 881 TTTLTWEESNAY YWQPYALPL 882 ESPLTWEESSAL YWQPYALPL 883 ETPLTWEESNAY YWQPYALPL 884 EATFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 888	QTPFTWEESNAY YWQPYALPL	876
QIPFTWEQSNAY YWQPYALPL 879 QAPLTWQESAAY YWQPYALPL 880 EPTFTWEESKAT YWQPYALPL 881 TTTLTWEESNAY YWQPYALPL 882 ESPLTWEESSAL YWQPYALPL 883 ETPLTWEESNAY YWQPYALPL 884 EATFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 887	ENPFTWQESNAY YWQPYALPL	877
QAPLTWQESAAY YWQPYALPL EPTFTWEESKAT YWQPYALPL 881 TTTLTWEESNAY YWQPYALPL 882 ESPLTWEESSAL YWQPYALPL 883 ETPLTWEESNAY YWQPYALPL 884 EATFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 888	VTPFTWEDSNVF YWQPYALPL	878
EPTFTWEESKAT YWQPYALPL 881 TTTLTWEESNAY YWQPYALPL 882 ESPLTWEESSAL YWQPYALPL 883 ETPLTWEESNAY YWQPYALPL 884 EATFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 888	QIPFTWEQSNAY YWQPYALPL	879
TTTLTWEESNAY YWQPYALPL 882 ESPLTWEESSAL YWQPYALPL 883 ETPLTWEESNAY YWQPYALPL 884 EATFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 888	QAPLTWQESAAY YWQPYALPL	880
TTTLTWEESNAY YWQPYALPL 882 ESPLTWEESSAL YWQPYALPL 883 ETPLTWEESNAY YWQPYALPL 884 EATFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 888	EPTFTWEESKAT YWQPYALPL	881
ESPLTWEESSAL YWQPYALPL 883 ETPLTWEESNAY YWQPYALPL 884 EATFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 888		882
ETPLTWEESNAY YWQPYALPL 884 EATFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 888		883
EATFTWAESNAY YWQPYALPL 885 EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 888		884
EALFTWKESTAY YWQPYALPL 886 STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 888		885
STP-TWEESNAY YWQPYALPL 887 ETPFTWEESNAY YWQPYALPL 888		886
ETPFTWEESNAY YWQPYALPL 888		887
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		889

STSFTWEESNAY YWQPYALPL	890
DSTFTWEESNAY YWQPYALPL	891
YIPFTWEESNAY YWQPYALPL	892
QTAFTWEESNAY YWQPYALPL	893
ETLFTWEESNAT YWQPYALPL	894
VSSFTWEESNAY YWQPYALPL	895
QPYALPL	896
Py-1-NapPYQJYALPL	897
TANVSSFEWTPG YWQPYALPL	898
FEWTPGYWQPYALPL	899
FEWTPGYWQJYALPL	900
FEWTPGYYQJYALPL	901
ETPFTWEESNAYYWQPYALPL	902
FTWEESNAYYWQJYALPL	903
ADVL YWQPYA PVTLWV	904
GDVAE YWQPYA LPLTSL	905
SWTDYG YWQPYA LPISGL	906
FEWTPGYWQPYALPL	911
FEWTPGYWQJYALPL	912
FEWTPGWYQPYALPL	913
FEWTPGWYQJYALPL	914
FEWTPGYYQPYALPL	915
FEWTPGYYQJYALPL	916
TANVSSFEWTPGYWQPYALPL	918
SWTDYGYWQPYALPISGL	919
ETPFTWEESNAYYWQPYALPL	920
ENTYSPNWADSMYWQPYALPL	921
SVGEDHNFWTSEYWQPYALPL	922
DGYDRWRQSGERYWQPYALPL	923
FEWTPGYWQPYALPL	924
FEWTPGYWQPY	925
FEWTPGYWQJY	926
EWTPGYWQPY	927
FEWTPGWYQJY	928
AEWTPGYWQJY	929
FAWTPGYWQJY	930
FEATPGYWQJY	931
FEWAPGYWQJY	932
FEWTAGYWQJY	933
FEWTPAYWQJY	934
FEWTPGAWQJY	935
FEWTPOYANO IA	936
FEWTPGYWQJA	937 938
FEWTGGYWQJY	939
FEWT IONNO IV	939
FEWTJGYWQJY	940
FEWTPecGYWQJY	941
FEWTPS-MWO IV	942
FEWTPSarWYQJY	943
FEWTSarGYWQJY	744

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AcFEWTPGYWQJY 1008 AcFEWTPGWYQJY 1009 AcFEWTPGYYQJY 1010 AcFEWTPaYWQJY 1011 AcFEWTPaYYQJY 1012 AcFEWTPGYYQJYALPL 1014 FEWTPGYWQJYALPL 1015 FEWTPGWYQJYALPL 1016 TANVSSFEWTPGYWQPYALPL 1017 AcFEWTPGYWQJY 1018 AcFEWTPGWYQJY 1019 AcFEWTPGYYQJY 1020 AcFEWTPAYWQJY 1021 AcFEWTPAWYQJY 1022	FEWTPGYYQJYALPL	1006
AcFEWTPGWYQJY 1009 AcFEWTPGYYQJY 1010 AcFEWTPaWWQJY 1011 AcFEWTPaWYQJY 1012 AcFEWTPaYYQJY 1013 FEWTPGYYQJYALPL 1014 FEWTPGWYQJYALPL 1015 FEWTPGWYQJYALPL 1016 TANVSSFEWTPGYWQPYALPL 1017 AcFEWTPGYWQJY 1018 AcFEWTPGWYQJY 1019 AcFEWTPGYYQJY 1020 AcFEWTPAYWQJY 1021 AcFEWTPAWYQJY 1022	FEWTPGYWQJY	1007
AcFEWTPGYYQJY 1010 AcFEWTPaYWQJY 1011 AcFEWTPaWYQJY 1012 AcFEWTPaYYQJY 1013 FEWTPGYYQJYALPL 1014 FEWTPGWQJYALPL 1015 FEWTPGWYQJYALPL 1016 TANVSSFEWTPGYWQPYALPL 1017 AcFEWTPGYWQJY 1018 AcFEWTPGWYQJY 1019 AcFEWTPGYYQJY 1020 AcFEWTPAYWQJY 1021 AcFEWTPAWYQJY 1022	AcFEWTPGYWQJY	1008
AcFEWTPaYWQJY 1011 AcFEWTPaWYQJY 1012 AcFEWTPaYYQJY 1013 FEWTPGYYQJYALPL 1014 FEWTPGYWQJYALPL 1015 FEWTPGWYQJYALPL 1016 TANVSSFEWTPGYWQPYALPL 1017 AcFEWTPGYWQJY 1018 AcFEWTPGWYQJY 1019 AcFEWTPGYYQJY 1020 AcFEWTPAYWQJY 1021 AcFEWTPAWYQJY 1022	AcFEWTPGWYQJY	1009
AcFEWTPaWYQJY 1012 AcFEWTPaYYQJY 1013 FEWTPGYYQJYALPL 1014 FEWTPGWYQJYALPL 1015 FEWTPGWYQJYALPL 1016 TANVSSFEWTPGYWQPYALPL 1017 AcFEWTPGYWQJY 1018 AcFEWTPGWYQJY 1019 AcFEWTPGYYQJY 1020 AcFEWTPAYWQJY 1021 AcFEWTPAWYQJY 1022	AcFEWTPGYYQJY	1010
AcFEWTPaYYQJY 1013 FEWTPGYYQJYALPL 1014 FEWTPGYWQJYALPL 1015 FEWTPGWYQJYALPL 1016 TANVSSFEWTPGYWQPYALPL 1017 AcFEWTPGYWQJY 1018 AcFEWTPGWYQJY 1019 AcFEWTPGYYQJY 1020 AcFEWTPAYWQJY 1021 AcFEWTPAWYQJY 1022	AcFEWTPaYWQJY	1011
FEWTPGYYQJYALPL 1014 FEWTPGYWQJYALPL 1015 FEWTPGWYQJYALPL 1016 TANVSSFEWTPGYWQPYALPL 1017 AcFEWTPGYWQJY 1018 AcFEWTPGWYQJY 1019 AcFEWTPGYYQJY 1020 AcFEWTPAYWQJY 1021 AcFEWTPAWYQJY 1022	AcFEWTPaWYQJY	1012
FEWTPGYWQJYALPL 1015 FEWTPGWYQJYALPL 1016 TANVSSFEWTPGYWQPYALPL 1017 AcFEWTPGYWQJY 1018 AcFEWTPGWYQJY 1019 AcFEWTPGYYQJY 1020 AcFEWTPAYWQJY 1021 AcFEWTPAWYQJY 1022	AcFEWTPaYYQJY	1013
FEWTPGWYQJYALPL 1016 TANVSSFEWTPGYWQPYALPL 1017 AcFEWTPGYWQJY 1018 AcFEWTPGWYQJY 1019 AcFEWTPGYYQJY 1020 AcFEWTPAYWQJY 1021 AcFEWTPAWYQJY 1022	FEWTPGYYQJYALPL	1014
TANVSSFEWTPGYWQPYALPL 1017 AcFEWTPGYWQJY 1018 AcFEWTPGWYQJY 1019 AcFEWTPGYYQJY 1020 AcFEWTPAYWQJY 1021 AcFEWTPAWYQJY 1022	FEWTPGYWQJYALPL	1015
AcFEWTPGYWQJY 1018 AcFEWTPGWYQJY 1019 AcFEWTPGYYQJY 1020 AcFEWTPAYWQJY 1021 AcFEWTPAWYQJY 1022	FEWTPGWYQJYALPL	1016
AcFEWTPGWYQJY 1019 AcFEWTPGYYQJY 1020 AcFEWTPAYWQJY 1021 AcFEWTPAWYQJY 1022	TANVSSFEWTPGYWQPYALPL	1017
AcFEWTPGYYQJY 1020 AcFEWTPAYWQJY 1021 AcFEWTPAWYQJY 1022	AcFEWTPGYWQJY	1018
AcFEWTPAYWQJY 1021 AcFEWTPAWYQJY 1022	AcFEWTPGWYQJY	1019
ACFEWTPAWYQJY 1022	AcFEWTPGYYQJY	
7.07 277 7.77 7.00	AcFEWTPAYWQJY	1021
AcFEWTPAYYQJY 1023		
	AcFEWTPAYYQJY	1023

Table 5—EPO-mimetic peptide sequences

Sequence/structure	SEQ
	ID NO:
YXCXXGPXTWXCXP	83
YXCXXGPXTWXCXP-YXCXXGPXTWXCXP	84
YXCXXGPXTWXCXP-A-YXCXXGPXTWXCXP	85
YXCXXGPXTWXCXP-Λ-(ε-amine)	86
βΑ YXCXXGPXTWXCXP-Λ- (α-amine)	. 86
GGTYSCHFGPLTWVCKPQGG	87
GGDYHCRMGPLTWVCKPLGG	88
GGVYACRMGPITWVCSPLGG	89
VGNYMCHFGPITWVCRPGGG	90
GGLYLCRFGPVTWDCGYKGG	91
GGTYSCHFGPLTWVCKPQGG- GGTYSCHFGPLTWVCKPQGG	92
GGTYSCHFGPLTWVCKPQGG -A- GGTYSCHFGPLTWVCKPQGG	93
GGTYSCHFGPLTWVCKPQGGSSK	94
GGTYSCHFGPLTWVCKPQGGSSK- GGTYSCHFGPLTWVCKPQGGSSK	95
GGTYSCHFGPLTWVCKPQGGSSK-A- GGTYSCHFGPLTWVCKPQGGSSK	96
GGTYSCHFGPLTWVCKPQGGSS (ε-amine)	97
βA	97
GGTYSCHFGPLTWVCKPQGGSS (α-amine) GGTYSCHFGPLTWVCKPQGGSSK(-Λ-biotin)	98
CX ₄ X ₅ GPX ₅ TWX ₇ C	421
GGTYSCHGPLTWVCKPQGG	422
VGNYMAHMGPITWVCRPGG	423 424
GGPHHVYACRMGPLTWIC	424
GGTYSCHFGPLTWVCKPQ	425
GGLYACHMGPMTWVCQPLRG	427
TIAQYICYMGPETWECRPSPKA YSCHFGPLTWVCK	428
	429
YCHFGPLTWVC X ₃ X ₄ X ₅ GPX ₆ TWX ₇ X ₈	124
YX,X,X,GPX,TWX,X,	461

X,YX ₂ X ₃ X ₄ X ₅ GPX ₅ TWX ₇ X ₈ X ₉ X ₁₀ X ₁₁	419
X,YX,CX,X,GPX,TWX,CX,X,,X,,	420
GGLYLCRFGPVTWDCGYKGG	1024
GGTYSCHFGPLTWVCKPQGG	1025
GGDYHCRMGPLTWVCKPLGG	1026
VGNYMCHFGPITWVCRPGGG	1029
GGVYACRMGPITWVCSPLGG	1030
VGNYMAHMGPITWVCRPGG	1035
GGTYSCHFGPLTWVCKPQ	1036
GGLYACHMGPMTWVCQPLRG	1037
TIAQYICYMGPETWECRPSPKA	1038
YSCHFGPLTWVCK	1039
YCHFGPLTWVC	1040
SCHFGPLTWVCK	1041
$(AX_2)_n X_3 X_4 X_5 GPX_6 TWX_7 X_8$	1042

Table 6—TPO-mimetic peptide sequences

Sequence/structure	SEQ ID NO:
IEGPTLRQWLAARA	13
IEGPTLRQWLAAKA	24
IEGPTLREWLAARA	25
IEGPTLRQWLAARA-A-IEGPTLRQWLAARA	26
IEGPTLRQWLAAKA-A-IEGPTLRQWLAAKA	27
IEGPTLRQCLAARA-A-IEGPTLRQCLAARA	28
L	20
IEGPTLRQWLAARA-Λ-K(BrAc)-Λ-IEGPTLRQWLAARA	29
IEGPTLRQWLAARA-Λ-Κ(PEG)-Λ-IEGPTLRQWLAARA	30
IEGPTLRQCLAARA-Λ-IEGPTLRQWLAARA	31
IEGPTLRQCLAARA-A-IEGPTLRQWLAARA	31
IEGPTLRQWLAARA-A-IEGPTLRQCLAARA	32
IEGPTLRQWLAARA-A-IEGPTLRQCLAARA	32
VRDQIXXXL	33
TLREWL	34
GRVRDQVAGW	35
GRVKDQIAQL	36
GVRDQVSWAL	37
ESVREQVMKY	38
SVRSQISASL	39
GVRETVYRHM	40
GVREVIVMHML GRVRDQIWAAL	41
AGVRDQILIWL	43
GRVRDQIMLSL	44
GRVRDQI(X),L	45
CTLRQWLQGC	46
CTLQEFLEGC	47
CTRTEWLHGC	48
CTLREWLHGGFC	49
CTLREWVFAGLC	50
CTLRQWLILLGMC	51
CTLAEFLASGVEQC	52
CSLQEFLSHGGYVC	53
CTLREFLDPTTAVC	54
CTLKEWLVSHEVWC	55
CTLREWL(X) ₂₄ C	56-60
REGPTLRQWM	61
EGPTLRQWLA	62
ERGPFWAKAC	63
REGPRCVMWM	64
CGTEGPTLSTWLDC	65

CEQDGPTLLEWLKC	66
CELVGPSLMSWLTC	67
CLTGPFVTQWLYEC	68
CRAGPTLLEWLTLC	69
CADGPTLREWISFC	70
C(X), EGPTLREWL(X), C	71-74
GGCTLREWLHGGFCGG	75
GGCADGPTLREWISFCGG	76
GNADGPTLRQWLEGRRPKN	77
LAIEGPTLRQWLHGNGRDT	78
HGRVGPTLREWKTQVATKK	79
TIKGPTLRQWLKSREHTS	80
ISDGPTLKEWLSVTRGAS	81
SIEGPTLREWLTSRTPHS	82

Table 7—G-CSF-mimetic peptide sequences

Sequence/structure	SEQ ID NO:
EEDCK	99
EEDCK	99
1 (1
EEDĊK	99
EEDoK	100
EEDoK	100
EEDoK	100
pGluEDσK	101
pGluEDσK	101
l' 1	!
pGluEDoK	101
PicSDoK	102
PicSDσK	102
PicSDoK	102
EEDCK-A-EEDCK	103
EEDXK-A-EEDXK	104

Table 8—TNF-antagonist peptide sequences

Sequence/structure	SEQ ID NO:
YCFTASENHCY	106
YCFTNSENHCY	107
YCFTRSENHCY	108
FCASENHCY	109
YCASENHCY	110
FCNSENHCY	111
FCNSENRCY	112
FCNSVENRCY	113
YCSQSVSNDCF	114
FCVSNDRCY	115
YCRKELGQVCY	116
YCKEPGQCY	117
YCRKEMGCY	118
FCRKEMGCY	119
YCWSQNLCY	120
YCELSQYLCY	121
YCWSQNYCY	122
YCWSQYLCY	123
DFLPHYKNTSLGHRP	1085
AA,-AB,	NR
· · · \	
AC	
/	
AA,-AB,	

Table 9—Integrin-binding peptide sequences

Sequence/structure	SEQ
004.02.00,012.00000	ID NO:
RX,ETX,WX,	441
RX,ETX,WX ₃	442
RGDGX	443
CRGDGXC	444
CX,X,RLDX,X,C	445
CARRLDAPC	446
CPSRLDSPC	447
X,X ₂ X ₃ RGDX ₄ X ₅ X ₆	448
CX,CRGDCX,C	449
CDCRGDCFC	450
CDCRGDCLC	451
CLCRGDCIC	452
X,X,DDX,X,X,X,	453
X,X,X,DDX,X,X,X,X,	454
CWDDGWLC	455
CWDDLWWLC	456
CWDDGLMC	457
CWDDGWMC	458
CSWDDGWLC	459
CPDDLWWLC	460
NGR	NR
GSL	NR
RGD	NR
CGRECPRLCQSSC	1071
CNGRCVSGCAGRC	1072
CLSGSLSC	1073
RGD	NR
NGR	NR
GSL	NR
NGRAHA	1074
CNGRC	1075
CDCRGDCFC	1076
CGSLVRC	1077
DLXXL	1043
RTDLDSLRTYTL	1044
RTDLDSLRTY	1053
RTDLDSLRT	1054
RTDLDSLR	1078
GDLDLLKLRLTL	1079
GDLHSLRQLLSR	1080
RDDLHMLRLQLW	1081
SSDLHALKKRYG	1082
RGDLKQLSELTW	1083
RGDLAALSAPPV	1084

Table 10—Selectin antagonist peptide sequences

Sequence/structure	SEQ ID NO:
DITWDQLWDLMK	147
DITWDELWKIMN	148
DYTWFELWDMMQ	149
QITWAQLWNMMK	150
DMTWHDLWTLMS	151
DYSWHDLWEMMS	152
EITWDQLWEVMN	153
HVSWEQLWDIMN	154
HITWDQLWRIMT	155
RNMSWLELWEHMK	156
AEWTWDQLWHVMNPAESQ	157
HRAEWLALWEQMSP	158
KKEDWLALWRIMSV	159
ITWDQLWDLMK	160
DITWDQLWDLMK	161
DITWDQLWDLMK	162
DITWDQLWDLMK	163
CONRYTDLVAIQNKNE	462
AENWADNEPNNKRNNED	463
RKNNKTWTWVGTKKALTNE	464
KKALTNEAENWAD	465
CQXRYTDLVAIQNKXE	466
RKXNXXWTWVGTXKXLTEE	467
AENWADGEPNNKXNXED	468
CXXXYTXLVAIQNKXE	469
RKXXXXWXWVGTXKXLTXE	470
AXNWXXXEPNNXXXED	471
XKXKTXEAXNWXX	472

Table 11—Antipathogenic peptide sequences

Sequence/structure	SEQ
- Ocquerice structure	ID NO:
GFFALIPKIISSPLFKTLLSAVGSALSSSGGQQ	503
GFFALIPKIISSPLFKTLLSAVGSALSSSGGQE	504
GFFALIPKIISSPLFKTLLSAV	505
GFFALIPKIISSPLFKTLLSAV	506
KGFFALIPKIISSPLFKTLLSAV	507
KKGFFALIPKIISSPLFKTLLSAV	508
KKGFFALIPKIISSPLFKTLLSAV	509
GFFALIPKIIS	510
GIGAVLKVLTTGLPALISWIKRKRQQ	511
GIGAVLKVLTTGLPALISWIKRKRQQ	512
GIGAVLKVLTTGLPALISWIKRKRQQ	513
GIGAVLKVLTTGLPALISWIKR	514
AVLKVLTTGLPALISWIKR	515
KLLLLKLLLK	516
KLLLKLLKLK	517
KLLLKLKLKLK	518
KKLLKLKLKK	519
KLLLKLLKLLK	520
KLLLKLKLKLK	521
KLLLLK	522
KLLLKLLK	523
KLLLKLKLK	524
KLLLKLKLKLK	525
KLLLKLKLKLK	526
KAAAKAAAKAAK	527
KVVVKVVVKVVK	528
KVVVKVKVKVVK	529
KVVVKVKVKVK	530
KVVVKVKVKVVK	531
KLILKL	532
KVLHLL	533
LKLRLL	534
KPLHLL	535
KLILKLVR	536
KVFHLLHL	537
HKFRILKL	538
KPFHILHL	539
KIIIKIKIKI	540
KIIIKIKIKIIK	541
KIIIKIKIKIK	542
KIPIKIKIKIPK	543
KIPIKIKIVK	544
RIIIRIRIRIR	545
RIIIRIRIRIR	546
RIIIRIRIRIR	547
RIVIRIRIRLIR	548

RIIVRIRLRIIR	549
RIGIRLRVRIIR	550
KIVIRIRIRLIR	551
RIAVKWRLRFIK	552
KIGWKLRVRIIR	553
KKIGWLIIRVRR	554
RIVIRIRIRIR	555
RIIVRIRLRIIRVR	556
RIGIRLRVRIIRRV	557
KIVIRIRARLIRIRIR	558
RIIVKIRLRIIKKIRL	559
KIGIKARVRIIRVKII	560
RIIVHIRLRIIHHIRL	561
HIGIKAHVRIIRVHII	562
RIYVKIHLRYIKKIRL	563
KIGHKARVHIIRYKII	564
RIYVKPHPRYIKKIRL	565
KPGHKARPHIIRYKII	566
KIVIRIRIRIRIRKIV	567
RIIVKIRLRIIKKIRLIKK	568
KIGWKLRVRIIRVKIGRLR	569
KIVIRIRIRIRIRIRKIVKVKRIR	570
RFAVKIRLRIIKKIRLIKKIRKRVIK	571
KAGWKLRVRIIRVKIGRLRKIGWKKRVRIK	572
RIYVKPHPRYIKKIRL	573
KPGHKARPHIIRYKII	574
KIVIRIRIRIRIRKIV	575
RIIVKIRLRIIKKIRLIKK	576
RIYVSKISIYIKKIRL	577
KIVIFTRIRLTSIRIRSIV	578
KPIHKARPTIIRYKMI	579
cyclicCKGFFALIPKIISSPLFKTLLSAVC	580
CKKGFFALIPKIISSPLFKTLLSAVC	581
CKKKGFFALIPKIISSPLFKTLLSAVC	582
CyclicCRIVIRIRIRLIRIRC	583
CyclicCKPGHKARPHIIRYKIIC	584
CyclicCRFAVKIRLRIIKKIRLIKKIRKRVIKC	585
KLLLKLLL KLLKC	586
KLLLKLLKLLK	587
KLLLKLKLKC	588
KLLLKLLK	589

Table 12—VIP-mimetic peptide sequences

Sequence/structure	SEQ
	ID NO:
HSDAVFYDNYTR LRKQMAVKKYLN SILN	590
NIE HSDAVFYDNYTR LRKQMAVKKYLN SILN	591
X ₁ X, ' X ₁ " X ₂	592
X ₃ S X ₄ LN	593
NH CH CO KKYX5 NH CH CO X6	594
(CH2)m Z (CH2)n	FOE
KKYL	595
NSILN	596
KKYL	597
KKYA	598
AVKKYL	599
NSILN	600
KKYV	601
SILauN	602
KKYLNie	603
NSYLN	604
NSIYN	605
KKYLPPNSILN	606
LauKKYL	607
CapKKYL	608
KYL	NR
KKYNle	609
VKKYL	610
LNSILN	611
YLNSILN	612
KKYLN	613
KKYLNS	614
KKYLNSI	615
KKYLNSIL	616
KKYL	617
KKYDA	618
AVKKYL	619
NSILN	620
KKYV	621
SILauN	622
NSYLN	623
NSIYN	624
KKYLNIe	625
KKYLPPNSILN	626
KKYL	627
KKYDA	628 -
AVKKYL	629
NSILN	630
KKYV	631
SILauN	632

LauKKYL	633
CapKKYL	634
KYL	NR
KYL	NR
KKYNle	635
VKKYL	636
LNSILN	637
	638
YLNSILN	639
KKYLNie	640
KKYLN	641
KKYLNS	642
KKYLNSI	643
KKYLNSIL	
KKKYLD	644 645
cyclicCKKYLC	
CKKYLK	646
S-CH ₂ -CO	647
KKYA	648
WWTDTGLW	649
WWTDDGLW	650
WWDTRGLWVWTI	651
FWGNDGIWLESG	652
DWDQFGLWRGAA	653
RWDDNGLWVVVL	654
SGMWSHYGIWMG	655
GGRWDQAGLWVA	656
KLWSEQGIWMGE	657
CWSMHGLWLC	658
GCWDNTGIWVPC	
DWDTRGLWVY	659
SLWDENGAWI	660
KWDDRGLWMH	661
QAWNERGLWT	662
QWDTRGLWVA	663
WNVHGIWQE	664
SWDTRGLWVE	665
DWDTRGLWVA	666
SWGRDGLWIE	667
EWTDNGLWAL	668
SWDEKGLWSA	669
SWDSSGLWMD	670

Table 13—Mdm/hdm antagonist peptide sequences

Sequence/structure	SEQ ID NO:
TFSDLW	130
QETFSDLWKLLP	131
QPTFSDLWKLLP	132
QETFSDYWKLLP	133
QPTFSDYWKLLP	134
MPRFMDYWEGLN	135
VQNFIDYWTQQF	136
TGPAFTHYWATF	137
IDRAPTFRDHWFALV	138
PRPALVFADYWETLY	139
PAFSRFWSDLSAGAH	140
PAFSRFWSKLSAGAH	141
PXFXDYWXXL	142
QETFSDLWKLLP	143
QPTFSDLWKLLP	144
QETFSDYWKLLP	145
QPTFSDYWKLLP	146

Table 14—Calmodulin antagonist peptide sequences

Sequence/structure	SEQ
•	ID NO:
SCVKWGKKEFCGS	164
SCWKYWGKECGS	165
SCYEWGKLRWCGS	166
SCLRWGKWSNCGS	167
SCWRWGKYQICGS	168
SCVSWGALKLCGS	169
SCIRWGQNTFCGS	170
SCWQWGNLKICGS	171
SCVRWGQLSICGS	172
LKKFNARRKLKGAILTTMLAK	173
RRWKKNFIAVSAANRFKK	174
RKWQKTGHAVRAIGRLSS	175
INLKALAALAKKIL	176
KIWSILAPLGTTLVKLVA	177
LKKLLKLLKKL	178
LKWKKLLKLLKKLL	179
AEWPSLTEIKTLSHFSV	180
AEWPSPTRVISTTYFGS	181
AELAHWPPVKTVLRSFT	182 "
AEGSWLQLLNLMKQMNN	183
AEWPSLTEIK	184

Table 15—Mast cell antagonists/Mast cell protease inhibitor peptide sequences

Sequence/structure	SEQ ID NO:
SGSGVLKRPLPILPVTR	272
RWLSSRPLPPLPLPPRT	273
GSGSYDTLALPSLPLHPMSS	274
GSGSYDTRALPSLPLHPMSS	275
GSGSSGVTMYPKLPPHWSMA	276
GSGSSGVRMYPKLPPHWSMA	277
GSGSSSMRMVPTIPGSAKHG	278
RNR	NR
QT	NR
RQK	NR
NRQ	NR
RQK	NR
RNRQKT	436
RNRQ	437
RNRQK	438
NRQKT	439
RQKT	440

Table 16—SH3 antagonist peptide sequences

Sequence/structure	SEQ
•	ID NO:
RPLPPLP	282
RELPPLP	283
SPLPPLP	284
GPLPPLP	285
RPLPIPP	286
RPLPIPP	287
RRLPPTP	288
ROLPPTP	289
RPLPSRP	290
RPLPTRP	291
SRLPPLP	292
RALPSPP	293
RRLPRTP	294
RPVPPIT	295
ILAPPVP	296
RPLPMLP	297
RPLPILP	298
RPLPSLP	299
RPLPSLP	300
RPLPMIP	301
RPLPLIP	302
RPLPPTP	303
RSLPPLP	304
RPQPPPP	305
RQLPIPP	306
XXXRPLPPLPXP	307
XXXRPLPPIPXX	308
XXXRPLPPLPXX	309
RXXRPLPPLPXP	310
RXXRPLPPLPPP	311
PPPYPPPPIPXX	312
PPPYPPPVPXX	313
LXXRPLPXYP	314
ΨXXRPLPXLP	315
РРХӨХРРРҰР	316
+PPYPXKPXWL	317
RPXΨРΨR+SXP	318
PPVPPRPXXTL	319
ЧР Ч Г РЧК	320
+@DXPLPXLP	321

Table 17—Somatostatin or cortistatin mimetic peptide sequences

Sequence/structure	SEQ
	ID NO:
X¹-X²-Asn-Phe-Phe-Trp-Lys-Thr-Phe-X³-Ser-X⁴	473
Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys	474
Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys	475
Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys	476
Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys	477
Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys	478
Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys	479
Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys	480
Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys	48 1
Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys	482
Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys	483
Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys	484
Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys	485
Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys	486
Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys	487
Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys	488
Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys	489
Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys	490
Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys	491
Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys	492
Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys	493
Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys	494
Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys	495
Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys	496
Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys	497

Table 18—UKR antagonist peptide sequences

Sequence/structure	SEQ ID NO:
AEPMPHSLNFSQYLWYT	196
AEHTYSSLWDTYSPLAF	197
AELDLWMRHYPLSFSNR	198
AESSLWTRYAWPSMPSY	199
AEWHPGLSFGSYLWSKT	200
AEPALLNWSFFFNPGLH	201
AEWSFYNLHLPEPQTIF	202
AEPLDLWSLYSLPPLAM	203
AEPTLWQLYQFPLRLSG	204
AEISFSELMWLRSTPAF	205
AELSEADLWTTWFGMGS	206
AESSLWRIFSPSALMMS	207
AESLPTLTSILWGKESV	208
AETLFMDLWHDKHILLT	209
AEILNFPLWHEPLWSTE	210
AESQTGTLNTLFWNTLR	211
AEPVYQYELDSYLRSYY	430
AELDLSTFYDIQYLLRT	431
AEFFKLGPNGYVYLHSA	432
FKLXXXGYVYL	433
AESTYHHLSLGYMYTLN	434
YHXLXXGYMYT	435

Table 19—Macrophage and/or
T-cell inhibiting peptide sequences

Sequence/structure	SEQ ID NO:
Xaa-Yaa-Arg	NR
Arg-Yaa-Xaa	NR
Xaa-Arg-Yaa	NR
Yaa-Arg-Xaa	NR
Ala-Arg	NR
	NR
Arg-Arg Asn-Arg	NR
	NR
Asp-Arg Cys-Arg	NR
Ciii 7 ug	NR NR
Glu-Arg	NR NR
Gly-Arg	NR NR
His-arg	NR NR
lle-Arg	NR NR
Leu-Arg	NR NR
Lys-Arg	
Met-Arg	NR NB
Phe-Arg	NR NB
Ser-Arg	NR NB
Thr-Arg	NR NB
Trp-Arg	NR Nm
Tyr-Arg	NR NTD
Val-Arg	NR
Ala-Glu-Arg	NR
Arg-Glu-Arg	NR
Asn-Glu-Arg	NR
Asp-Glu-Arg	NR
Cys-Glu-Arg	NR
Gin-Glu-Arg	NR
Glu-Glu-Arg	NR
Gly-Glu-Arg	NR
His-Glu-Arg	NR
lle-Glu-Arg	NR NR
Leu-Glu-Arg	NR
Lys-Glu-Arg	NR
Met-Glu-Arg	NR
Phe-Glu-Arg	NR
Pro-Glu-Arg	NR
Ser-Glu-Arg	NR
Thr-Glu-Arg	NR
	NR
Trp-Glu-Arg	NR NR
Tyr-Glu-Arg Val-Glu-Arg	NR NR

Arg-Ala	NR
Arg-Asp	NR
Arg-Cys	NR
Arg-Gin	NR
Arg-Glu	NR
Arg-Gly	NR
Arg-His	NR
Arg-lie	NR
Arg-Leu	NR
Arg-Lys	NR
Arg-Met	NR
Arg-Phe	NR
Arg-Pro	NR
Arg-Ser	NR
Arg-Thr	NR
Arg-Trp	NR ***
Arg-Tyr	NR
Arg-Val	NR
Arg-Glu-Ala	NR
Arg-Glu-Asn	NR
Arg-Glu-Asp	NR
Arg-Glu-Cys	NR
Arg-Glu-Gln	NR
Arg-Glu-Glu	NR
Arg-Glu-Gly	NR
Arg-Glu-His	NR
Arg-Glu-Ile	NR
Arg-Glu-Leu	NR
Arg-Glu-Lys	NR
Arg-Glu-Met	NR
Arg-Glu-Phe	NR
Arg-Glu-Pro	NR
Arg-Glu-Ser	NR
Arg-Glu-Thr	NR
Arg-Glu-Trp	NR
Arg-Glu-Tyr	NR
Arg-Glu-Val	NR
Ala-Arg-Glu	NR
Arg-Arg-Glu	NR
Asn-Arg-Glu	NR
Asp-Arg-Glu	NR
Cys-Arg-Glu	NR
Gln-Arg-Glu	NR
Glu-Arg-Glu	NR
Gly-Arg-Glu	NR
His-Arg-Glu	- NR
Ile-Arg-Glu	NR
Leu-Arg-Glu	NR
Lys-Arg-Glu	NR
Met-Arg-Glu	NR

Phe-Arg-Glu	NR
Pro-Arg-Glu	NR
Ser-Arg-Glu	NR
Thr-Arg-Glu	NR
Trp-Arg-Glu	NR
Tyr-Arg-Glu	NR
Val-Arg-Glu	NR
Glu-Arg-Ala,	NR
Glu-Arg-Arg	NR
Glu-Arg-Asn	NR
Glu-Arg-Asp	NR
Glu-Arg-Cys	NR
Glu-Arg-Gln	NR
Glu-Arg-Gly	NR
Glu-Arg-His	NR
Glu-Arg-lie	NR
Glu-Arg-Leu	NR
Glu-Arg-Lys	NR
Glu-Arg-Met	NR
Glu-Arg-Phe	NR
Glu-Arg-Pro	NR
Glu-Arg-Ser	NR
Glu-Arg-Thr	NR
Glu-Arg-Trp	NR
Glu-Arg-Tyr	NR
Glu-Arg-Val	NR

Table 20—Additional Exemplary Pharmacologically Active Peptides

Sequence/structure	SEQ ID NO:	Activity
VEPNCDIHVMWEWECFERL	1027	VEGF-antagonist
GERWCFDGPLTWVCGEES	1084	VEGF-antagonist
RGWVEICVADDNGMCVTEAQ	1085	VEGF-antagonist
GWDECDVARMWEWECFAGV	1086	VEGF- antagonist
GERWCFDGPRAWVCGWEI	501	VEGF- antagonist
EELWCFDGPRAWVCGYVK	502	VEGF- antagonist
RGWVEICAADDYGRCLTEAQ	1031	VEGF- antagonist
RGWVEICESDVWGRCL	1087	VEGF- antagonist
RGWVEICESDVWGRCL	1088	VEGF- antagonist
GGNECDIARMWEWECFERL	1089	VEGF- antagonist
RGWVEICAADDYGRCL	1090	VEGF-antagonist
CTTHWGFTLC	1028	MMP inhibitor
CLRSGXGC	1091	MMP inhibitor
CXXHWGFXXC	1092	MMP inhibitor
CXPXC	1093	MMP inhibitor
CRRHWGFEFC	1094	MMP inhibitor
STTHWGFTLS	1095	MMP inhibitor
CSLHWGFWWC	1096	CTLA4-mimetic
GFVCSGIFAVGVGRC	125	CTLA4-mimetic
APGVRLGCAVLGRYC	126	CTLA4-mimetic
LLGRMK	105	Antiviral (HBV)
ICVVQDWGHHRCTAGHMANLTSHASAI	127	C3b antagonist
ICVVQDWGHHRCT	128	C3b antagonist
CVVQDWGHHAC	129	C3b antagonist
STGGFDDVYDWARGVSSALTTTLVATR	185	Vinculin-binding
STGGFDDVYDWARRVSSALTTTLVATR	186	Vinculin-binding
SRGVNFSEWLYDMSAAMKEASNVFPSRRSR	187	Vinculin-binding
SSQNWDMEAGVEDLTAAMLGLLSTIHSSSR	188	Vinculin-binding
SSPSLYTQFLVNYESAATRIQDLLIASRPSR	189	Vinculin-binding
SSTGWVDLLGALQRAADATRTSIPPSLQNSR	190	Vinculin-binding
DVYTKKELIECARRVSEK	191	Vinculin-binding
EKGSYYPGSGIAQFHIDYNNVS	192	C4BP-binding
SGIAQFHIDYNNVSSAEGWHVN	193	C4BP-binding
LVTVEKGSYYPGSGIAQFHIDYNNVSSAEGWHVN	194	C4BP-binding
SGIAQFHIDYNNVS	195	C4BP-binding
LLGRMK	279	anti-HBV
ALLGRMKG	280	anti-HBV
LDPAFR	281	anti-HBV
CXXRGDC	322	Inhibition of platelet aggregation
DDI DDI D	323	Src antagonist
RPLPPLP	324	Src antagonist
PPVPPR	325	Anti-cancer
XFXDXWXXLXX	020	(particularly for

KACRRLFGPVDSEQLSRDCD RERWNFDFVTETPLEGDFAW RRRQTSMTDFYHSKRRLIFS 328 p16-mimetic STSMTDFYHSKRRLIFSKRKP 329 p16-mimetic RRLIF RRLIF RRLIF RRLIFSRQIKIWFQNRRMKWKK 330 p16-mimetic KRRQTSATDFYHSKRRLIFSRQIKIWFQNRRMKWKK 331 p16-mimetic KRRLIFSKRQIKIWFQNRRMKWKK 332 p16-mimetic KRRLIFSKRQIKIWFQNRRMKWKK 332 p16-mimetic CASIN Gliy Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Phe Gln Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Gly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val WHWRHRIPLQLAAGR 1097 Carbohydrate (GD1 alpha) mimetic LKTPRV 1098 β2GPl Ab binding NTLKTPRV 1099 β2GPl Ab binding NTLKTPRVGGC
RERWNFDFVTETPLEGDFAW 327 p16-mimetic KRRQTSMTDFYHSKRRLIFS 328 p16-mimetic TSMTDFYHSKRRLIFSKRKP 329 p16-mimetic RRLIF 330 p16-mimetic KRRQTSATDFYHSKRRLIFSRQIKIWFQNRRMKWKK 331 p16-mimetic KRRLIFSKRQIKIWFQNRRMKWKK 332 p16-mimetic Asn Gln Gly Arg His Phe Cys Gly Gly Ala Leu lle His Ala 498 CAP37 mimetic/LPS binding Arg Phe Val Met Thr Ala Ala Ser Cys Phe Gln 499 CAP37 mimetic/LPS binding Met Thr Ala Ala Ser Cys 500 CAP37 mimetic/LPS binding Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val 500 CAP37 mimetic/LPS binding WHWRHRIPLQLAAGR 1097 carbohydrate (GD1 alpha) mimetic LKTPRV 1098 β2GPI Ab binding NTLKTPRVGGC 1100 β2GPI Ab binding
KRRQTSMTDFYHSKRRLIFS328p16-mimeticTSMTDFYHSKRRLIFSKRKP329p16-mimeticRRLIF330p16-mimeticKRRQTSATDFYHSKRRLIFSRQIKIWFQNRRMKWKK331p16-mimeticKRRLIFSKRQIKIWFQNRRMKWKK332p16-mimeticAsn Gln Gly Arg His Phe Cys Gly Gly Ala Leu lle His Ala498CAP37 mimetic/LPSArg Phe Val Met Thr Ala Ala Ser Cys Phe Gln500CAP37 mimetic/LPSMet Thr Ala Ala Ser Cys500CAP37 mimetic/LPSGly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val500CAP37 mimetic/LPSWHWRHRIPLQLAAGR1097carbohydrate (GD1 alpha) mimeticLKTPRV1098β2GPl Ab bindingNTLKTPRV1099β2GPl Ab bindingNTLKTPRVGGC1100β2GPl Ab binding
TSMTDFYHSKRRLIFSKRKP RRLIF RRLIF KRRQTSATDFYHSKRRLIFSRQIKIWFQNRRMKWKK Asn Gln Gly Arg His Phe Cys Gly Gly Ala Leu lle His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Phe Gln Arg His Phe Cys Gly Gly Ala Leu lle His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Gly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val WHWRHRIPLQLAAGR 1097 Carbohydrate (GD1 alpha) mimetic LKTPRV NTLKTPRV 1098 β2GPI Ab binding NTLKTPRVGGC
RRLIF KRRQTSATDFYHSKRRLIFSRQIKIWFQNRRMKWKK KRRLIFSKRQIKIWFQNRRMKWKK Asn Gln Gly Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Phe Gln Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Gly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val WHWRHRIPLQLAAGR 1097 Carbohydrate (GD1 alpha) mimetic LKTPRV NTLKTPRV NTLKTPRVGGC 1100 B2GPI Ab binding NTLKTPRVGGC
KRRQTSATDFYHSKRRLIFSRQIKIWFQNRRMKWKK KRRLIFSKRQIKIWFQNRRMKWKK Asn Gln Gly Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Phe Gln Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Gly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val WHWRHRIPLQLAAGR 1097 Carbohydrate (GD1 alpha) mimetic LKTPRV NTLKTPRV NTLKTPRVGGC 1100 B2GPI Ab binding
KRRLIFSKRQIKIWFQNRRMKWKK332p16-mimeticAsn Gln Gly Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Phe Gln498CAP37 mimetic/LPS bindingArg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys499CAP37 mimetic/LPS bindingGly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val500CAP37 mimetic/LPS bindingWHWRHRIPLQLAAGR1097carbohydrate (GD1 alpha) mimeticLKTPRV1098β2GPI Ab bindingNTLKTPRV1099β2GPI Ab bindingNTLKTPRVGGC1100β2GPI Ab binding
Asn Gln Gly Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Phe Gln Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Gly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val WHWRHRIPLQLAAGR 1097 Carbohydrate (GD1 alpha) mimetic LKTPRV 1098 NTLKTPRV 1099 B2GPI Ab binding NTLKTPRVGGC 1100 B2GPI Ab binding
Arg Phe Val Met Thr Ala Ala Ser Cys Phe Gln Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Gly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val WHWRHRIPLQLAAGR 1097 Carbohydrate (GD1 alpha) mimetic LKTPRV NTLKTPRV NTLKTPRVGGC 1100 Binding CAP37 mimetic/LPS binding Carbohydrate (GD1 alpha) mimetic
Arg His Phe Cys Gly Gly Ala Leu lle His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Gly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val WHWRHRIPLQLAAGR 1097 Carbohydrate (GD1 alpha) mimetic LKTPRV 1098 NTLKTPRV 1099 B2GPI Ab binding NTLKTPRVGGC 1100 B2GPI Ab binding
Met Thr Ala Ala Ser CysbindingGly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val500CAP37 mimetic/LPS bindingWHWRHRIPLQLAAGR1097carbohydrate (GD1 alpha) mimeticLKTPRV1098β2GPI Ab bindingNTLKTPRV1099β2GPI Ab bindingNTLKTPRVGGC1100β2GPI Ab binding
Gly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val WHWRHRIPLQLAAGR 1097 carbohydrate (GD1 alpha) mimetic LKTPRV 1098 β2GPI Ab binding NTLKTPRV 1099 β2GPI Ab binding NTLKTPRVGGC
Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val WHWRHRIPLQLAAGR 1097 carbohydrate (GD1 alpha) mimetic LKTPRV 1098 β2GPI Ab binding NTLKTPRV NTLKTPRVGGC 1100 β2GPI Ab binding
WHWRHRIPLQLAAGR 1097 carbohydrate (GD1 alpha) mimetic LKTPRV 1098 β2GPI Ab binding NTLKTPRV 1099 β2GPI Ab binding NTLKTPRVGGC 1100 β2GPI Ab binding
LKTPRV 1098 β2GPI Ab binding NTLKTPRV 1099 β2GPI Ab binding NTLKTPRVGGC 1100 β2GPI Ab binding
LKTPRV1098β2GPI Ab bindingNTLKTPRV1099β2GPI Ab bindingNTLKTPRVGGC1100β2GPI Ab binding
NTLKTPRV1099β2GPI Ab bindingNTLKTPRVGGC1100β2GPI Ab binding
NTLKTPRV1099β2GPI Ab bindingNTLKTPRVGGC1100β2GPI Ab binding
NTLKTPRVGGC 1100 β2GPI Ab binding
KDKATF 1101 β2GPI Ab binding
KDKATFGCHD 1102 β2GPI Ab binding
KDKATFGCHDGC 1103 β2GPl Ab binding
TLRVYK 1104 β2GPI Ab binding
ATLRVYKGG 1105 B2GPI Ab binding
CATLRVYKGG 1106 β2GPI Ab binding
INLKALAALAKKIL 1107 Membrane-
transporting
GWT NR Membrane-
transporting
GWTLNSAGYLLG 1108 Membrane-
transporting
GWTLNSAGYLLGKINLKALAALAKKIL 1109 Membrane-
transporting

The present invention is also particularly useful with peptides having activity in treatment of:

 cancer, wherein the peptide is a VEGF-mimetic or a VEGF receptor antagonist, a HER2 agonist or antagonist, a CD20 antagonist and the like;

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- asthma, wherein the protein of interest is a CKR3 antagonist, an IL-5 receptor antagonist, and the like;
- thrombosis, wherein the protein of interest is a GPIIb antagonist, a
 GPIIIa antagonist, and the like;

 autoimmune diseases and other conditions involving immune modulation, wherein the protein of interest is an IL-2 receptor antagonist, a CD40 agonist or antagonist, a CD40L agonist or antagonist, a thymopoietin mimetic and the like.

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<u>Vehicles</u>. This invention requires the presence of at least one vehicle (F¹, F²) attached to a peptide through the N-terminus, C-terminus or a sidechain of one of the amino acid residues. Multiple vehicles may also be used; e.g., Fc's at each terminus or an Fc at a terminus and a PEG group at the other terminus or a sidechain.

An Fc domain is the preferred vehicle. The Fc domain may be fused to the N or C termini of the peptides or at both the N and C termini. For the TPO-mimetic peptides, molecules having the Fc domain fused to the N terminus of the peptide portion of the molecule are more bioactive than other such fusions, so fusion to the N terminus is preferred.

As noted above, Fc variants are suitable vehicles within the scope of this invention. A native Fc may be extensively modified to form an Fc variant in accordance with this invention, provided binding to the salvage receptor is maintained; see, for example WO 97/34631 and WO 96/32478. In such Fc variants, one may remove one or more sites of a native Fc that provide structural features or functional activity not required by the fusion molecules of this invention. One may remove these sites by, for example, substituting or deleting residues, inserting residues into the site, or truncating portions containing the site. The inserted or substituted residues may also be altered amino acids, such as peptidomimetics or Damino acids. Fc variants may be desirable for a number of reasons, several of which are described below. Exemplary Fc variants include molecules and sequences in which:

1. Sites involved in disulfide bond formation are removed. Such removal may avoid reaction with other cysteine-containing proteins present in

the host cell used to produce the molecules of the invention. For this purpose, the cysteine-containing segment at the N-terminus may be truncated or cysteine residues may be deleted or substituted with other amino acids (e.g., alanyl, seryl). In particular, one may truncate the N-terminal 20-amino acid segment of SEQ ID NO: 2 or delete or substitute the cysteine residues at positions 7 and 10 of SEQ ID NO: 2. Even when cysteine residues are removed, the single chain Fc domains can still form a dimeric Fc domain that is held together non-covalently.

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- 2. A native Fc is modified to make it more compatible with a selected host cell. For example, one may remove the PA sequence near the N-terminus of a typical native Fc, which may be recognized by a digestive enzyme in <u>E. coli</u> such as proline iminopeptidase. One may also add an N-terminal methionine residue, especially when the molecule is expressed recombinantly in a bacterial cell such as <u>E. coli</u>. The Fc domain of SEQ ID NO: 2 (Figure 4) is one such Fc variant.
 - 3. A portion of the N-terminus of a native Fc is removed to prevent N-terminal heterogeneity when expressed in a selected host cell. For this purpose, one may delete any of the first 20 amino acid residues at the N-terminus, particularly those at positions 1, 2, 3, 4 and 5.
- 4. One or more glycosylation sites are removed. Residues that are typically glycosylated (e.g., asparagine) may confer cytolytic response. Such residues may be deleted or substituted with unglycosylated residues (e.g., alanine).
- 5. Sites involved in interaction with complement, such as the C1q binding site, are removed. For example, one may delete or substitute the EKK sequence of human IgG1. Complement recruitment may not be advantageous for the molecules of this invention and so may be avoided with such an Fc variant.

6. Sites are removed that affect binding to Fc receptors other than a salvage receptor. A native Fc may have sites for interaction with certain white blood cells that are not required for the fusion molecules of the present invention and so may be removed.

- 7. The ADCC site is removed. ADCC sites are known in the art; see, for example, <u>Molec. Immunol</u>. 29 (5): 633-9 (1992) with regard to ADCC sites in IgG1. These sites, as well, are not required for the fusion molecules of the present invention and so may be removed.
- 8. When the native Fc is derived from a non-human antibody, the native Fc may be humanized. Typically, to humanize a native Fc, one will substitute selected residues in the non-human native Fc with residues that are normally found in human native Fc. Techniques for antibody humanization are well known in the art.

Preferred Fc variants include the following. In SEQ ID NO: 2

(Figure 4) the leucine at position 15 may be substituted with glutamate; the glutamate at position 99, with alanine; and the lysines at positions 101 and 103, with alanines. In addition, one or more tyrosine residues can be replaced by phenyalanine residues.

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An alternative vehicle would be a protein, polypeptide, peptide, antibody, antibody fragment, , or small molecule (e.g., a peptidomimetic compound) capable of binding to a salvage receptor. For example, one could use as a vehicle a polypeptide as described in U.S. Pat. No. 5,739,277, issued April 14, 1998 to Presta et al. Peptides could also be selected by phage display for binding to the FcRn salvage receptor. Such salvage receptor-binding compounds are also included within the meaning of "vehicle" and are within the scope of this invention. Such vehicles should be selected for increased half-life (e.g., by avoiding sequences recognized by proteases) and decreased immunogenicity (e.g., by favoring non-immunogenic sequences, as discovered in antibody humanization).

As noted above, polymer vehicles may also be used for F¹ and F². Various means for attaching chemical moieties useful as vehicles are currently available, see, e.g., Patent Cooperation Treaty ("PCT") International Publication No. WO 96/11953, entitled "N-Terminally Chemically Modified Protein Compositions and Methods," herein incorporated by reference in its entirety. This PCT publication discloses, among other things, the selective attachment of water soluble polymers to the N-terminus of proteins.

A preferred polymer vehicle is polyethylene glycol (PEG). The PEG group may be of any convenient molecular weight and may be linear or branched. The average molecular weight of the PEG will preferably range from about 2 kiloDalton ("kD") to about 100 kDa, more preferably from about 5 kDa to about 50 kDa, most preferably from about 5 kDa to about 10 kDa. The PEG groups will generally be attached to the compounds of the invention via acylation or reductive alkylation through a reactive group on the PEG moiety (e.g., an aldehyde, amino, thiol, or ester group) to a reactive group on the inventive compound (e.g., an aldehyde, amino, or ester group).

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A useful strategy for the PEGylation of synthetic peptides consists of combining, through forming a conjugate linkage in solution, a peptide and a PEG moiety, each bearing a special functionality that is mutually reactive toward the other. The peptides can be easily prepared with conventional solid phase synthesis (see, for example, Figures 5 and 6 and the accompanying text herein). The peptides are "preactivated" with an appropriate functional group at a specific site. The precursors are purified and fully characterized prior to reacting with the PEG moiety. Ligation of the peptide with PEG usually takes place in aqueous phase and can be easily monitored by reverse phase analytical HPLC. The PEGylated peptides can be easily purified by preparative HPLC and characterized by

analytical HPLC, amino acid analysis and laser desorption mass spectrometry.

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Polysaccharide polymers are another type of water soluble polymer which may be used for protein modification. Dextrans are polysaccharide polymers comprised of individual subunits of glucose predominantly linked by $\alpha 1$ -6 linkages. The dextran itself is available in many molecular weight ranges, and is readily available in molecular weights from about 1 kD to about 70 kD. Dextran is a suitable water soluble polymer for use in the present invention as a vehicle by itself or in combination with another vehicle (e.g., Fc). See, for example, WO 96/11953 and WO 96/05309. The use of dextran conjugated to therapeutic or diagnostic immunoglobulins has been reported; see, for example, European Patent Publication No. 0 315 456, which is hereby incorporated by reference. Dextran of about 1 kD to about 20 kD is preferred when dextran is used as a vehicle in accordance with the present invention.

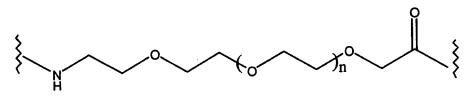
Linkers. Any "linker" group is optional. When present, its chemical structure is not critical, since it serves primarily as a spacer. The linker is preferably made up of amino acids linked together by peptide bonds. Thus, in preferred embodiments, the linker is made up of from 1 to 20 amino acids linked by peptide bonds, wherein the amino acids are selected from the 20 naturally occurring amino acids. Some of these amino acids may be glycosylated, as is well understood by those in the art. In a more preferred embodiment, the 1 to 20 amino acids are selected from glycine, alanine, proline, asparagine, glutamine, and lysine. Even more preferably, a linker is made up of a majority of amino acids that are sterically unhindered, such as glycine and alanine. Thus, preferred linkers are polyglycines (particularly (Gly)4, (Gly)5), poly(Gly-Ala), and polyalanines. Other specific examples of linkers are:

(Gly)₃Lys(Gly)₄ (SEQ ID NO: 333);

(Gly)₃AsnGlySer(Gly)₂ (SEQ ID NO: 334); (Gly)₃Cys(Gly)₄ (SEQ ID NO: 335); and GlyProAsnGlyGly (SEQ ID NO: 336).

To explain the above nomenclature, for example, (Gly)₃Lys(Gly)₄ means Gly-Gly-Gly-Gly-Gly-Gly-Gly. Combinations of Gly and Ala are also preferred. The linkers shown here are exemplary; linkers within the scope of this invention may be much longer and may include other residues.

Non-peptide linkers are also possible. For example, alkyl linkers such as -NH-(CH_2) $_s$ -C(O)-, wherein s = 2-20 could be used. These alkyl linkers may further be substituted by any non-sterically hindering group such as lower alkyl (e.g., C_1 - C_6) lower acyl, halogen (e.g., Cl, Br), CN, NH $_2$, phenyl, etc. An exemplary non-peptide linker is a PEG linker, VI



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wherein n is such that the linker has a molecular weight of 100 to 5000 kD, preferably 100 to 500 kD. The peptide linkers may be altered to form derivatives in the same manner as described above.

Derivatives. The inventors also contemplate derivatizing the
peptide and/or vehicle portion of the compounds. Such derivatives may
improve the solubility, absorption, biological half life, and the like of the
compounds. The moieties may alternatively eliminate or attenuate any
undesirable side-effect of the compounds and the like. Exemplary
derivatives include compounds in which:

The compound or some portion thereof is cyclic. For example, the
peptide portion may be modified to contain two or more Cys residues
(e.g., in the linker), which could cyclize by disulfide bond formation.

For citations to references on preparation of cyclized derivatives, see Table 2.

2. The compound is cross-linked or is rendered capable of cross-linking between molecules. For example, the peptide portion may be modified to contain one Cys residue and thereby be able to form an intermolecular disulfide bond with a like molecule. The compound may also be cross-linked through its C-terminus, as in the molecule shown below.

VII

$$F^{1}-(X^{1})_{b}-CO-N$$
 NH_{2}
 $F^{1}-(X^{1})_{b}-CO-N$
 NH_{2}

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- 4. One or more peptidyl [-C(O)NR-] linkages (bonds) is replaced by a non-peptidyl linkage. Exemplary non-peptidyl linkages are -CH₂-carbamate [-CH₂-OC(O)NR-], phosphonate, -CH₂-sulfonamide [-CH₂-S(O)₂NR-], urea [-NHC(O)NH-], -CH₂-secondary amine, and alkylated peptide [-C(O)NR⁶- wherein R⁶ is lower alkyl].
- 5. The N-terminus is derivatized. Typically, the N-terminus may be acylated or modified to a substituted amine. Exemplary N-terminal derivative groups include -NRR¹ (other than -NH₂), -NRC(O)R¹, -NRC(O)OR¹, -NRS(O)₂R¹, -NHC(O)NHR¹, succinimide, or benzyloxycarbonyl-NH- (CBZ-NH-), wherein R and R¹ are each independently hydrogen or lower alkyl and wherein the phenyl ring may be substituted with 1 to 3 substituents selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_4 alkoxy, chloro, and bromo.
- 6. The free C-terminus is derivatized. Typically, the C-terminus is esterified or amidated. For example, one may use methods described in the art to add (NH-CH₂-CH₂-NH₂)₂ to compounds of this invention

having any of SEQ ID NOS: 504 to 508 at the C-terminus. Likewise, one may use methods described in the art to add -NH₂ to compounds of this invention having any of SEQ ID NOS: 924 to 955, 963 to 972, 1005 to 1013, or 1018 to 1023 at the C-terminus. Exemplary C-terminal derivative groups include, for example, -C(O)R² wherein R² is lower alkoxy or -NR³R⁴ wherein R³ and R⁴ are independently hydrogen or C₁-C₈ alkyl (preferably C_1 -C₄ alkyl).

7. A disulfide bond is replaced with another, preferably more stable, cross-linking moiety (e.g., an alkylene). See, e.g., Bhatnagar et al. (1996), J. Med. Chem. 39: 3814-9; Alberts et al. (1993) Thirteenth Am. Pep. Symp., 357-9.

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- One or more individual amino acid residues is modified. Various derivatizing agents are known to react specifically with selected sidechains or terminal residues, as described in detail below.
- Lysinyl residues and amino terminal residues may be reacted with succinic or other carboxylic acid anhydrides, which reverse the charge of the lysinyl residues. Other suitable reagents for derivatizing alpha-amino-containing residues include imidoesters such as methyl picolinimidate; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid; O-methylisourea; 2,4 pentanedione; and transaminase-catalyzed reaction with glyoxylate.

Arginyl residues may be modified by reaction with any one or combination of several conventional reagents, including phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginyl residues requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

Specific modification of tyrosyl residues has been studied extensively, with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidizole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively.

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Carboxyl sidechain groups (aspartyl or glutamyl) may be selectively modified by reaction with carbodiimides (R'-N=C=N-R') such as 1-cyclohexyl-3-(2-morpholinyl-(4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues may be converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

Glutaminyl and asparaginyl residues may be deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues falls within the scope of this invention.

Cysteinyl residues can be replaced by amino acid residues or other moieties either to eliminate disulfide bonding or, conversely, to stabilize cross-linking. See, e.g., Bhatnagar <u>et al.</u> (1996), <u>J. Med. Chem.</u> 39: 3814-9.

Derivatization with bifunctional agents is useful for cross-linking the peptides or their functional derivatives to a water-insoluble support matrix or to other macromolecular vehicles. Commonly used cross-linking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(p-azidophenyl)dithiolpropioimidate yield photoactivatable intermediates that are capable of forming crosslinks in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates

and the reactive substrates described in U.S. Pat. Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440 are employed for protein immobilization.

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Carbohydrate (oligosaccharide) groups may conveniently be attached to sites that are known to be glycosylation sites in proteins. Generally, O-linked oligosaccharides are attached to serine (Ser) or threonine (Thr) residues while N-linked oligosaccharides are attached to asparagine (Asn) residues when they are part of the sequence Asn-X-Ser/Thr, where X can be any amino acid except proline. X is preferably one of the 19 naturally occurring amino acids other than proline. The structures of N-linked and O-linked oligosaccharides and the sugar residues found in each type are different. One type of sugar that is commonly found on both is N-acetylneuraminic acid (referred to as sialic acid). Sialic acid is usually the terminal residue of both N-linked and Olinked oligosaccharides and, by virtue of its negative charge, may confer acidic properties to the glycosylated compound. Such site(s) may be incorporated in the linker of the compounds of this invention and are preferably glycosylated by a cell during recombinant production of the polypeptide compounds (e.g., in mammalian cells such as CHO, BHK, COS). However, such sites may further be glycosylated by synthetic or semi-synthetic procedures known in the art.

Other possible modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, oxidation of the sulfur atom in Cys, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains. Creighton, Proteins: Structure and Molecule Properties (W. H. Freeman & Co., San Francisco), pp. 79-86 (1983).

Compounds of the present invention may be changed at the DNA level, as well. The DNA sequence of any portion of the compound may be

changed to codons more compatible with the chosen host cell. For <u>E. coli</u>, which is the preferred host cell, optimized codons are known in the art. Codons may be substituted to eliminate restriction sites or to include silent restriction sites, which may aid in processing of the DNA in the selected host cell. The vehicle, linker and peptide DNA sequences may be modified to include any of the foregoing sequence changes.

Methods of Making

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The compounds of this invention largely may be made in transformed host cells using recombinant DNA techniques. To do so, a recombinant DNA molecule coding for the peptide is prepared. Methods of preparing such DNA molecules are well known in the art. For instance, sequences coding for the peptides could be excised from DNA using suitable restriction enzymes. Alternatively, the DNA molecule could be synthesized using chemical synthesis techniques, such as the phosphoramidate method. Also, a combination of these techniques could be used.

The invention also includes a vector capable of expressing the peptides in an appropriate host. The vector comprises the DNA molecule that codes for the peptides operatively linked to appropriate expression control sequences. Methods of effecting this operative linking, either before or after the DNA molecule is inserted into the vector, are well known. Expression control sequences include promoters, activators, enhancers, operators, ribosomal binding sites, start signals, stop signals, cap signals, polyadenylation signals, and other signals involved with the control of transcription or translation.

The resulting vector having the DNA molecule thereon is used to transform an appropriate host. This transformation may be performed using methods well known in the art.

Any of a large number of available and well-known host cells may be used in the practice of this invention. The selection of a particular host is dependent upon a number of factors recognized by the art. These include, for example, compatibility with the chosen expression vector, toxicity of the peptides encoded by the DNA molecule, rate of transformation, ease of recovery of the peptides, expression characteristics, bio-safety and costs. A balance of these factors must be struck with the understanding that not all hosts may be equally effective for the expression of a particular DNA sequence. Within these general guidelines, useful microbial hosts include bacteria (such as <u>E. coli</u> sp.), yeast (such as <u>Saccharomyces</u> sp.) and other fungi, insects, plants, mammalian (including human) cells in culture, or other hosts known in the art.

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Next, the transformed host is cultured and purified. Host cells may be cultured under conventional fermentation conditions so that the desired compounds are expressed. Such fermentation conditions are well known in the art. Finally, the peptides are purified from culture by methods well known in the art.

The compounds may also be made by synthetic methods. For example, solid phase synthesis techniques may be used. Suitable techniques are well known in the art, and include those described in Merrifield (1973), Chem. Polypeptides, pp. 335-61 (Katsoyannis and Panayotis eds.); Merrifield (1963), J. Am. Chem. Soc. 85: 2149; Davis et al. (1985), Biochem. Intl. 10: 394-414; Stewart and Young (1969), Solid Phase Peptide Synthesis; U.S. Pat. No. 3,941,763; Finn et al. (1976), The Proteins (3rd ed.) 2: 105-253; and Erickson et al. (1976), The Proteins (3rd ed.) 2: 257-527. Solid phase synthesis is the preferred technique of making individual peptides since it is the most cost-effective method of making small peptides.

Compounds that contain derivatized peptides or which contain non-peptide groups may be synthesized by well-known organic chemistry techniques.

Uses of the Compounds

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In general. The compounds of this invention have pharmacologic activity resulting from their ability to bind to proteins of interest as agonists, mimetics or antagonists of the native ligands of such proteins of interest. The utility of specific compounds is shown in Table 2. The activity of these compounds can be measured by assays known in the art. For the TPO-mimetic and EPO-mimetic compounds, <u>in vivo</u> assays are further described in the Examples section herein.

In addition to therapeutic uses, the compounds of the present invention are useful in diagnosing diseases characterized by dysfunction of their associated protein of interest. In one embodiment, a method of detecting in a biological sample a protein of interest (e.g., a receptor) that is capable of being activated comprising the steps of: (a) contacting the sample with a compound of this invention; and (b) detecting activation of the protein of interest by the compound. The biological samples include tissue specimens, intact cells, or extracts thereof. The compounds of this invention may be used as part of a diagnostic kit to detect the presence of their associated proteins of interest in a biological sample. Such kits employ the compounds of the invention having an attached label to allow for detection. The compounds are useful for identifying normal or abnormal proteins of interest. For the EPO-mimetic compounds, for example, presence of abnormal protein of interest in a biological sample may be indicative of such disorders as Diamond Blackfan anemia, where it is believed that the EPO receptor is dysfunctional.

Therapeutic uses of EPO-mimetic compounds. The EPO-mimetic compounds of the invention are useful for treating disorders characterized by low red blood cell levels. Included in the invention are methods of modulating the endogenous activity of an EPO receptor in a mammal, preferably methods of increasing the activity of an EPO receptor. In

general, any condition treatable by erythropoietin, such as anemia, may also be treated by the EPO-mimetic compounds of the invention. These compounds are administered by an amount and route of delivery that is appropriate for the nature and severity of the condition being treated and may be ascertained by one skilled in the art. Preferably, administration is by injection, either subcutaneous, intramuscular, or intravenous.

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Therapeutic uses of TPO-mimetic compounds. For the TPO-mimetic compounds, one can utilize such standard assays as those described in WO95/26746 entitled "Compositions and Methods for Stimulating Megakaryocyte Growth and Differentiation". In vivo assays also appear in the Examples hereinafter.

The conditions to be treated are generally those that involve an existing megakaryocyte/platelet deficiency or an expected megakaryocyte/platelet deficiency (e.g., because of planned surgery or platelet donation). Such conditions will usually be the result of a deficiency (temporary or permanent) of active Mpl ligand in vivo. The generic term for platelet deficiency is thrombocytopenia, and hence the methods and compositions of the present invention are generally available for treating thrombocytopenia in patients in need thereof.

Thrombocytopenia (platelet deficiencies) may be present for various reasons, including chemotherapy and other therapy with a variety of drugs, radiation therapy, surgery, accidental blood loss, and other specific disease conditions. Exemplary specific disease conditions that involve thrombocytopenia and may be treated in accordance with this invention are: aplastic anemia, idiopathic thrombocytopenia, metastatic tumors which result in thrombocytopenia, systemic lupus erythematosus, splenomegaly, Fanconi's syndrome, vitamin B12 deficiency, folic acid deficiency, May-Hegglin anomaly, Wiskott-Aldrich syndrome, and paroxysmal nocturnal hemoglobinuria. Also, certain treatments for AIDS

result in thrombocytopenia (e.g., AZT). Certain wound healing disorders might also benefit from an increase in platelet numbers.

With regard to anticipated platelet deficiencies, e.g., due to future surgery, a compound of the present invention could be administered several days to several hours prior to the need for platelets. With regard to acute situations, e.g., accidental and massive blood loss, a compound of this invention could be administered along with blood or purified platelets.

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The TPO-mimetic compounds of this invention may also be useful in stimulating certain cell types other than megakaryocytes if such cells are found to express Mpl receptor. Conditions associated with such cells that express the Mpl receptor, which are responsive to stimulation by the Mpl ligand, are also within the scope of this invention.

The TPO-mimetic compounds of this invention may be used in any situation in which production of platelets or platelet precursor cells is desired, or in which stimulation of the c-Mpl receptor is desired. Thus, for example, the compounds of this invention may be used to treat any condition in a mammal wherein there is a need of platelets, megakaryocytes, and the like. Such conditions are described in detail in the following exemplary sources: WO95/26746; WO95/21919; WO95/18858; WO95/21920 and are incorporated herein.

The TPO-mimetic compounds of this invention may also be useful in maintaining the viability or storage life of platelets and/or megakaryocytes and related cells. Accordingly, it could be useful to include an effective amount of one or more such compounds in a composition containing such cells.

The therapeutic methods, compositions and compounds of the present invention may also be employed, alone or in combination with other cytokines, soluble Mpl receptor, hematopoietic factors, interleukins, growth factors or antibodies in the treatment of disease states

characterized by other symptoms as well as platelet deficiencies. It is anticipated that the inventive compound will prove useful in treating some forms of thrombocytopenia in combination with general stimulators of hematopoiesis, such as IL-3 or GM-CSF. Other megakaryocytic stimulatory factors, i.e., meg-CSF, stem cell factor (SCF), leukemia inhibitory factor (LIF), oncostatin M (OSM), or other molecules with megakaryocyte stimulating activity may also be employed with Mpl ligand. Additional exemplary cytokines or hematopoietic factors for such co-administration include IL-1 alpha, IL-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-11, colony stimulating factor-1 (CSF-1), SCF, GM-CSF, granulocyte 10 colony stimulating factor (G-CSF), EPO, interferon-alpha (IFN-alpha), consensus interferon, IFN-beta, or IFN-gamma. It may further be useful to administer, either simultaneously or sequentially, an effective amount of a soluble mammalian Mpl receptor, which appears to have an effect of causing megakaryocytes to fragment into platelets once the 15 megakaryocytes have reached mature form. Thus, administration of an inventive compound (to enhance the number of mature megakaryocytes) followed by administration of the soluble Mpl receptor (to inactivate the ligand and allow the mature megakaryocytes to produce platelets) is expected to be a particularly effective means of stimulating platelet 20 production. The dosage recited above would be adjusted to compensate for such additional components in the therapeutic composition. Progress of the treated patient can be monitored by conventional methods.

In cases where the inventive compounds are added to compositions of platelets and/or megakaryocytes and related cells, the amount to be included will generally be ascertained experimentally by techniques and assays known in the art. An exemplary range of amounts is 0.1 µg—1 mg inventive compound per 106 cells.

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Pharmaceutical Compositions

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In General. The present invention also provides methods of using pharmaceutical compositions of the inventive compounds. Such pharmaceutical compositions may be for administration for injection, or for oral, pulmonary, nasal, transdermal or other forms of administration. In general, the invention encompasses pharmaceutical compositions comprising effective amounts of a compound of the invention together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol); incorporation of the material into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hyaluronic acid may also be used, and this may have the effect of promoting sustained duration in the circulation. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712 which are herein incorporated by reference. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilized form. Implantable sustained release formulations are also contemplated, as are transdermal formulations.

Oral dosage forms. Contemplated for use herein are oral solid dosage forms, which are described generally in Chapter 89 of Remington's Pharmaceutical Sciences (1990), 18th Ed., Mack Publishing Co. Easton PA 18042, which is herein incorporated by reference. Solid dosage forms include tablets, capsules, pills, troches or lozenges, cachets or pellets. Also,

liposomal or proteinoid encapsulation may be used to formulate the present compositions (as, for example, proteinoid microspheres reported in U.S. Patent No. 4,925,673). Liposomal encapsulation may be used and the liposomes may be derivatized with various polymers (e.g., U.S. Patent No. 5,013,556). A description of possible solid dosage forms for the therapeutic is given in Chapter 10 of Marshall, K., Modern Pharmaceutics (1979), edited by G. S. Banker and C. T. Rhodes, herein incorporated by reference. In general, the formulation will include the inventive compound, and inert ingredients which allow for protection against the stomach environment, and release of the biologically active material in the intestine.

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Also specifically contemplated are oral dosage forms of the above inventive compounds. If necessary, the compounds may be chemically modified so that oral delivery is efficacious. Generally, the chemical modification contemplated is the attachment of at least one moiety to the compound molecule itself, where said moiety permits (a) inhibition of proteolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the compound and increase in circulation time in the body. Moieties useful as covalently attached vehicles in this invention may also be used for this purpose. Examples of such moieties include: PEG, copolymers of ethylene glycol and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone and polyproline. See, for example, Abuchowski and Davis, Soluble Polymer-Enzyme Adducts, Enzymes as Drugs (1981), Hocenberg and Roberts, eds., Wiley-Interscience, New York, NY,, pp 367-83; Newmark, et al. (1982), J. Appl. Biochem. 4:185-9. Other polymers that could be used are poly-1,3-dioxolane and poly-1,3,6-tioxocane. Preferred for pharmaceutical usage, as indicated above, are PEG moieties.

For oral delivery dosage forms, it is also possible to use a salt of a modified aliphatic amino acid, such as sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), as a carrier to enhance absorption of the therapeutic compounds of this invention. The clinical efficacy of a heparin formulation using SNAC has been demonstrated in a Phase II trial conducted by Emisphere Technologies. See US Patent No. 5,792,451, "Oral drug delivery composition and methods".

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The compounds of this invention can be included in the formulation as fine multiparticulates in the form of granules or pellets of particle size about 1 mm. The formulation of the material for capsule administration could also be as a powder, lightly compressed plugs or even as tablets. The therapeutic could be prepared by compression.

Colorants and flavoring agents may all be included. For example, the protein (or derivative) may be formulated (such as by liposome or microsphere encapsulation) and then further contained within an edible product, such as a refrigerated beverage containing colorants and flavoring agents.

One may dilute or increase the volume of the compound of the invention with an inert material. These diluents could include carbohydrates, especially mannitol, α -lactose, anhydrous lactose, cellulose, sucrose, modified dextrans and starch. Certain inorganic salts may also be used as fillers including calcium triphosphate, magnesium carbonate and sodium chloride. Some commercially available diluents are Fast-Flo, Emdex, STA-Rx 1500, Emcompress and Avicell.

Disintegrants may be included in the formulation of the therapeutic into a solid dosage form. Materials used as disintegrants include but are not limited to starch including the commercial disintegrant based on starch, Explotab. Sodium starch glycolate, Amberlite, sodium carboxymethylcellulose, ultramylopectin, sodium alginate, gelatin, orange

peel, acid carboxymethyl cellulose, natural sponge and bentonite may all be used. Another form of the disintegrants are the insoluble cationic exchange resins. Powdered gums may be used as disintegrants and as binders and these can include powdered gums such as agar, Karaya or tragacanth. Alginic acid and its sodium salt are also useful as disintegrants.

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Binders may be used to hold the therapeutic agent together to form a hard tablet and include materials from natural products such as acacia, tragacanth, starch and gelatin. Others include methyl cellulose (MC), ethyl cellulose (EC) and carboxymethyl cellulose (CMC). Polyvinyl pyrrolidone (PVP) and hydroxypropylmethyl cellulose (HPMC) could both be used in alcoholic solutions to granulate the therapeutic.

An antifrictional agent may be included in the formulation of the therapeutic to prevent sticking during the formulation process. Lubricants may be used as a layer between the therapeutic and the die wall, and these can include but are not limited to; stearic acid including its magnesium and calcium salts, polytetrafluoroethylene (PTFE), liquid paraffin, vegetable oils and waxes. Soluble lubricants may also be used such as sodium lauryl sulfate, magnesium lauryl sulfate, polyethylene glycol of various molecular weights, Carbowax 4000 and 6000.

Glidants that might improve the flow properties of the drug during formulation and to aid rearrangement during compression might be added. The glidants may include starch, talc, pyrogenic silica and hydrated silicoaluminate.

To aid dissolution of the compound of this invention into the aqueous environment a surfactant might be added as a wetting agent. Surfactants may include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents might be used and could include benzalkonium chloride or

benzethonium chloride. The list of potential nonionic detergents that could be included in the formulation as surfactants are lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. These surfactants could be present in the formulation of the protein or derivative either alone or as a mixture in different ratios.

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Additives may also be included in the formulation to enhance uptake of the compound. Additives potentially having this property are for instance the fatty acids oleic acid, linoleic acid and linolenic acid.

Controlled release formulation may be desirable. The compound of this invention could be incorporated into an inert matrix which permits release by either diffusion or leaching mechanisms e.g., gums. Slowly degenerating matrices may also be incorporated into the formulation, e.g., alginates, polysaccharides. Another form of a controlled release of the compounds of this invention is by a method based on the Oros therapeutic system (Alza Corp.), i.e., the drug is enclosed in a semipermeable membrane which allows water to enter and push drug out through a single small opening due to osmotic effects. Some enteric coatings also have a delayed release effect.

Other coatings may be used for the formulation. These include a variety of sugars which could be applied in a coating pan. The therapeutic agent could also be given in a film coated tablet and the materials used in this instance are divided into 2 groups. The first are the nonenteric materials and include methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, methylhydroxy-ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-methyl cellulose, sodium carboxy-methyl cellulose, providone and the polyethylene glycols. The second group consists of the enteric materials that are commonly esters of phthalic acid.

A mix of materials might be used to provide the optimum film coating. Film coating may be carried out in a pan coater or in a fluidized bed or by compression coating.

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Pulmonary delivery forms. Also contemplated herein is pulmonary delivery of the present protein (or derivatives thereof). The protein (or derivative) is delivered to the lungs of a mammal while inhaling and traverses across the lung epithelial lining to the blood stream. (Other reports of this include Adjei et al., Pharma. Res. (1990) 7: 565-9; Adjei et al. (1990), Internatl. J. Pharmaceutics 63: 135-44 (leuprolide acetate); Braquet et al. (1989), J. Cardiovasc. Pharmacol. 13 (suppl.5): s.143-146 (endothelin-1); Hubbard et al. (1989), Annals Int. Med. 3: 206-12 (α1-antitrypsin); Smith et al. (1989), J. Clin. Invest. 84: 1145-6 (α1-proteinase); Oswein et al. (March 1990), "Aerosolization of Proteins", Proc. Symp. Resp. Drug Delivery II, Keystone, Colorado (recombinant human growth hormone); Debs et al. (1988), J. Immunol. 140: 3482-8 (interferon-γ and tumor necrosis factor α) and Platz et al., U.S. Patent No. 5,284,656 (granulocyte colony stimulating factor).

Contemplated for use in the practice of this invention are a wide range of mechanical devices designed for pulmonary delivery of therapeutic products, including but not limited to nebulizers, metered dose inhalers, and powder inhalers, all of which are familiar to those skilled in the art. Some specific examples of commercially available devices suitable for the practice of this invention are the Ultravent nebulizer, manufactured by Mallinckrodt, Inc., St. Louis, Missouri; the Acorn II nebulizer, manufactured by Marquest Medical Products, Englewood, Colorado; the Ventolin metered dose inhaler, manufactured by Glaxo Inc., Research Triangle Park, North Carolina; and the Spinhaler powder inhaler, manufactured by Fisons Corp., Bedford, Massachusetts.

All such devices require the use of formulations suitable for the dispensing of the inventive compound. Typically, each formulation is specific to the type of device employed and may involve the use of an appropriate propellant material, in addition to diluents, adjuvants and/or carriers useful in therapy.

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The inventive compound should most advantageously be prepared in particulate form with an average particle size of less than 10 μm (or microns), most preferably 0.5 to 5 μm , for most effective delivery to the distal lung.

Pharmaceutically acceptable carriers include carbohydrates such as trehalose, mannitol, xylitol, sucrose, lactose, and sorbitol. Other ingredients for use in formulations may include DPPC, DOPE, DSPC and DOPC. Natural or synthetic surfactants may be used. PEG may be used (even apart from its use in derivatizing the protein or analog). Dextrans, such as cyclodextran, may be used. Bile salts and other related enhancers may be used. Cellulose and cellulose derivatives may be used. Amino acids may be used, such as use in a buffer formulation.

Also, the use of liposomes, microcapsules or microspheres, inclusion complexes, or other types of carriers is contemplated.

Formulations suitable for use with a nebulizer, either jet or ultrasonic, will typically comprise the inventive compound dissolved in water at a concentration of about 0.1 to 25 mg of biologically active protein per mL of solution. The formulation may also include a buffer and a simple sugar (e.g., for protein stabilization and regulation of osmotic pressure). The nebulizer formulation may also contain a surfactant, to reduce or prevent surface induced aggregation of the protein caused by atomization of the solution in forming the aerosol.

Formulations for use with a metered-dose inhaler device will generally comprise a finely divided powder containing the inventive

compound suspended in a propellant with the aid of a surfactant. The propellant may be any conventional material employed for this purpose, such as a chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrocluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-tetrafluoroethane, or combinations thereof. Suitable surfactants include sorbitan trioleate and soya lecithin. Oleic acid may also be useful as a surfactant.

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Formulations for dispensing from a powder inhaler device will comprise a finely divided dry powder containing the inventive compound and may also include a bulking agent, such as lactose, sorbitol, sucrose, mannitol, trehalose, or xylitol in amounts which facilitate dispersal of the powder from the device, e.g., 50 to 90% by weight of the formulation.

Nasal delivery forms. Nasal delivery of the inventive compound is also contemplated. Nasal delivery allows the passage of the protein to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung. Formulations for nasal delivery include those with dextran or cyclodextran. Delivery via transport across other mucous membranes is also contemplated.

<u>Dosages</u>. The dosage regimen involved in a method for treating the above-described conditions will be determined by the attending physician, considering various factors which modify the action of drugs, e.g. the age, condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors. Generally, the daily regimen should be in the range of 0.1-1000 micrograms of the inventive compound per kilogram of body weight, preferably 0.1-150 micrograms per kilogram.

Specific preferred embodiments

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The inventors have determined preferred peptide sequences for molecules having many different kinds of activity. The inventors have further determined preferred structures of these preferred peptides combined with preferred linkers and vehicles. Preferred structures for these preferred peptides listed in Table 21 below.

Table 21—Preferred embodiments

Sequence/structure	SEQ	Activity
-	ID	
	NO:	
F'-(G),-IEGPTLRQWLAARA-(G),-IEGPTLRQWLAARA	337	TPO-mimetic
IEGPTLRQWLAARA-(G) _s -IEGPTLRQWLAARA-(G) ₅ - F'	338	TPO-mimetic
F'-(G) ₅ -IEGPTLRQWLAARA	ł	TPO-mimetic
	1032	
IEGPTLRQWLAARA -(G)₅- F'	1033	TPO-mimetic
F'-(G) ₅ -GGTYSCHFGPLTWVCKPQGG-(G) ₄ -	339	EPO-mimetic
GGTYSCHFGPLTWVCKPQGG		
GGTYSCHFGPLTWVCKPQGG-(G),-		EPO-mimetic
GGTYSCHFGPLTWVCKPQGG-(G),-F1	340	
GGTYSCHFGPLTWVCKPQGG-(G),-F1		EPO-mimetic
	1034	
F¹-(G)₅-DFLPHYKNTSLGHRP	1045	TNF-α inhibitor
DFLPHYKNTSLGHRP-(G),-F1	4044	TNF-α inhibitor
	1046	
F¹-(G) ₅ - FEWTPGYWQPYALPL	1047	IL-1 R antagonist
FEWTPGYWQPYALPL-(G),-F'	1047	IL-1 R antagonist
FEW IPG TWQPTALPL-(G)5-P	1048	ic in antagonist
F'-(G) _s -VEPNCDIHVMWEWECFERL		VEGF-antagonist
(5/5) 2. (100) (110)	1049	
VEPNCDIHVMWEWECFERL-(G) ₅ -F ¹		VEGF-antagonist
, ,,,	1050	-
F'-(G) ₅ -CTTHWGFTLC		MMP inhibitor
	1051	
CTTHWGFTLC-(G)₅-F¹		MMP inhibitor
	1052	

[&]quot;F" is an Fc domain as defined previously herein.

"Working examples

The compounds described above may be prepared as described below. These examples comprise preferred embodiments of the invention and are illustrative rather than limiting.

Example 1

TPO-Mimetics

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The following example uses peptides identified by the numbers appearing in Table A hereinafter.

Preparation of peptide 19. Peptide 17b (12 mg) and MeO-PEG-SH 5000 (30 mg, 2 equiv.) were dissolved in 1 ml aqueous buffer (pH 8). The mixture was incubated at RT for about 30 minutes and the reaction was checked by analytical HPLC, which showed a > 80% completion of the reaction. The pegylated material was isolated by preparative HPLC.

Preparation of peptide 20. Peptide 18 (14 mg) and MeO-PEG-maleimide (25 mg) were dissolved in about 1.5 ml aqueous buffer (pH 8). The mixture was incubated at RT for about 30 minutes, at which time about 70% transformation was complete as monitored with analytical HPLC by applying an aliquot of sample to the HPLC column. The pegylated material was purified by preparative HPLC.

Bioactivity assay. The TPO in vitro bioassay is a mitogenic assay utilizing an IL-3 dependent clone of murine 32D cells that have been transfected with human mpl receptor. This assay is described in greater detail in WO 95/26746. Cells are maintained in MEM medium containing 10% Fetal Clone II and 1 ng/ml mIL-3. Prior to sample addition, cells are prepared by rinsing twice with growth medium lacking mIL-3. An extended twelve point TPO standard curve is prepared, ranging from 33 to 39 pg/ml. Four dilutions, estimated to fall within the linear portion of the standard curve, (100 to 125 pg/ml), are prepared for each sample and run in triplicate. A volume of 100 µl of each dilution of sample or standard is added to appropriate wells of a 96 well microtiter plate

containing 10,000 cells/well. After forty-four hours at 37 °C and 10% CO₂, MTS (a tetrazolium compound which is bioreduced by cells to a formazan) is added to each well. Approximately six hours later, the optical density is read on a plate reader at 490 nm. A dose response curve (log TPO concentration vs. O.D.- Background) is generated and linear regression analysis of points which fall in the linear portion of the standard curve is performed. Concentrations of unknown test samples are determined using the resulting linear equation and a correction for the dilution factor.

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TMP tandem repeats with polyglycine linkers. Our design of sequentially linked TMP repeats was based on the assumption that a dimeric form of TMP was required for its effective interaction with c-Mpl (the TPO receptor) and that depending on how they were wound up against each other in the receptor context, the two TMP molecules could be tethered together in the C- to N-terminus configuration in a way that would not perturb the global dimeric conformation. Clearly, the success of the design of tandem linked repeats depends on proper selection of the length and composition of the linker that joins the C- and N-termini of the two sequentially aligned TMP monomers. Since no structural information of the TMP bound to c-Mpl was available, a series of repeated peptides with linkers composed of 0 to 10 and 14 glycine residues (Table A) were synthesized. Glycine was chosen because of its simplicity and flexibility, based on the rationale that a flexible polyglycine peptide chain might allow for the free folding of the two tethered TMP repeats into the required conformation, while other amino acid sequences may adopt undesired secondary structures whose rigidity might disrupt the correct packing of the repeated peptide in the receptor context.

The resulting peptides are readily accessible by conventional solid phase peptide synthesis methods (Merrifield (1963), <u>I. Amer. Chem. Soc.</u> 85: 2149) with either Fmoc or t-Boc chemistry. Unlike the synthesis of the

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C-terminally linked parallel dimer which required the use of an orthogonally protected lysine residue as the initial branch point to build the two peptide chains in a pseudosymmetrical way (Cwirla et al. (1997), Science 276: 1696-9), the synthesis of these tandem repeats was a straightforward, stepwise assembly of the continuous peptide chains from the C- to N-terminus. Since dimerization of TMP had a more dramatic effect on the proliferative activity than binding affinity as shown for the Cterminal dimer (Cwirla et al. (1997)), the synthetic peptides were tested directly for biological activity in a TPO-dependent cell-proliferation assay using an IL-3 dependent clone of murine 32D cells transfected with the full-length c-Mpl (Palacios et al., Cell 41:727 (1985)). As the test results showed, all the polyglycine linked tandem repeats demonstrated >1000 fold increases in potency as compared to the monomer, and were even more potent than the C-terminal dimer in this cell proliferation assay. The absolute activity of the C-terminal dimer in our assay was lower than that of the native TPO protein, which is different from the previously reported findings in which the C-terminal dimer was found to be as active as the natural ligand (Cwirla et al. (1997)). This might be due to differences in the conditions used in the two assays. Nevertheless, the difference in activity between tandem (C terminal of first monomer linked to N terminal of second monomer) and C-terminal (C terminal of first monomer linked to C terminal of second monomer; also referred to as parallel) dimers in the same assay clearly demonstrated the superiority of tandem repeat strategy over parallel peptide dimerization. It is interesting to note that a wide range of length is tolerated by the linker. The optimal linker between tandem peptides with the selected TMP monomers apparently is composed of 8 glycines.

Other tandem repeats. Subsequent to this first series of TMP tandem repeats, several other molecules were designed either with

different linkers or containing modifications within the monomer itself. The first of these molecules, peptide 13, has a linker composed of GPNG, a sequence known to have a high propensity to form a β -turn-type secondary structure. Although still about 100-fold more potent than the monomer, this peptide was found to be >10-fold less active than the equivalent GGGG-linked analog. Thus, introduction of a relatively rigid β -turn at the linker region seemed to have caused a slight distortion of the optimal agonist conformation in this short linker form.

The Trp9 in the TMP sequence is a highly conserved residue among the active peptides isolated from random peptide libraries. There is also a 10 highly conserved Trp in the consensus sequences of EPO mimetic peptides and this Trp residue was found to be involved in the formation of a hydrophobic core between the two EMPs and contributed to hydrophobic interactions with the EPO receptor. Livnah et al. (1996), Science 273: 464-71). By analogy, the Trp9 residue in TMP might have a similar function in 15 dimerization of the peptide ligand, and as an attempt to modulate and estimate the effects of noncovalent hydrophobic forces exerted by the two indole rings, several analogs were made resulting from mutations at the Trp. So in peptide 14, the Trp residue was replaced in each of the two TMP monomers with a Cys, and an intramolecular disulfide bond was 20 formed between the two cysteines by oxidation which was envisioned to mimic the hydrophobic interactions between the two Trp residues in peptide dimerization. Peptide 15 is the reduced form of peptide 14. In peptide 16, the two Trp residues were replaced by Ala. As the assay data show, all three analogs were inactive. These data further demonstrated 25 that Trp is critical for the activity of the TPO mimetic peptide, not just for dimer formation.

The next two peptides (peptide 17a, and 18) each contain in their 8amino acid linker a Lys or Cys residue. These two compounds are

precursors to the two PEGylated peptides (peptide 19 and 20) in which the side chain of the Lys or Cys is modified by a PEG moiety. A PEG moiety was introduced at the middle of a relatively long linker, so that the large PEG component (5 kDa) is far enough away from the critical binding sites in the peptide molecule. PEG is a known biocompatible polymer which is increasingly used as a covalent modifier to improve the pharmacokinetic profiles of peptide- and protein-based therapeutics.

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A modular, solution-based method was devised for convenient PEGylation of synthetic or recombinant peptides. The method is based on the now well established chemoselective ligation strategy which utilizes the specific reaction between a pair of mutually reactive functionalities. So, for pegylated peptide 19, the lysine side chain was preactivated with a bromoacetyl group to give peptide 17b to accommodate reaction with a thiol-derivatized PEG. To do that, an orthogonal protecting group, Dde, was employed for the protection of the lysine ϵ -amine. Once the whole peptide chain was assembled, the N-terminal amine was reprotected with t-Boc. Dde was then removed to allow for the bromoacetylation. This strategy gave a high quality crude peptide which was easily purified using conventional reverse phase HPLC. Ligation of the peptide with the thiolmodified PEG took place in aqueous buffer at pH 8 and the reaction completed within 30 minutes. MALDI-MS analysis of the purified, pegylated material revealed a characteristic, bell-shaped spectrum with an increment of 44 Da between the adjacent peaks. For PEG-peptide 20, a cysteine residue was placed in the linker region and its side chain thiol group would serve as an attachment site for a maleimide-containing PEG. Similar conditions were used for the pegylation of this peptide. As the assay data revealed, these two pegylated peptides had even higher in vitro bioactivity as compared to their unpegylated counterparts.

Peptide 21 has in its 8-amino acid linker a potential glycosylation motif, NGS. Since our exemplary tandem repeats are made up of natural amino acids linked by peptide bonds, expression of such a molecule in an appropriate eukaryotic cell system should produce a glycopeptide with the carbohydrate moiety added on the side chain carboxyamide of Asn. Glycosylation is a common post-translational modification process which can have many positive impacts on the biological activity of a given protein by increasing its aqueous solubility and in vivo stability. As the assay data show, incorporation of this glycosylation motif into the linker maintained high bioactivity. The synthetic precursor of the potential glycopeptide had in effect an activity comparable to that of the -(G)₈-linked analog. Once glycosylated, this peptide is expected to have the same order of activity as the pegylated peptides, because of the similar chemophysical properties exhibited by a PEG and a carbohydrate moiety.

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The last peptide is a dimer of a tandem repeat. It was prepared by oxidizing peptide 18, which formed an intermolecular disulfide bond between the two cysteine residues located at the linker. This peptide was designed to address the possibility that TMP was active as a tetramer. The assay data showed that this peptide was not more active than an average tandem repeat on an adjusted molar basis, which indirectly supports the idea that the active form of TMP is indeed a dimer, otherwise dimerization of a tandem repeat would have a further impact on the bioactivity.

In order to confirm the in vitro data in animals, one pegylated TMP tandem repeat (compound 20 in Table A) was delivered subcutaneously to normal mice via osmotic pumps. Time and dose-dependent increases were seen in platelet numbers for the duration of treatment. Peak platelet levels over 4-fold baseline were seen on day 8. A dose of 10 µg/kg/day of the pegylated TMP repeat produced a similar response to rHuMGDF (non-pegylated) at 100 µg/kg/day delivered by the same route.

Table A—TPO-mimetic Peptides

Peptide	Compound	SEQ ID	Relative	
No.		NO:	Potency	
	TPO	·	++++	
	TMP monomer	13	+	
	TMP C-C dimer		+++-	
TMP-(G) _n -	TMP:			
1	n = 0	341	++++-	
2	n = 1	342	++++	
3	n = 2	343	++++	
4	n = 3	344	++++	
5	n = 4	345	++++	
.6	n = 5	346	++++	
7	n = 6	347	++++	
8	n = 7	348	++++	
9	n = 8	349	++++-	
10	n = 9	350	++++	
11	n = 10	351	++++	
12	n = 14	352	++++	
13	TMP-GPNG-TMP	353	+++	
14	IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA	354		
15	(cyclic) IEGPTLRQCLAARA-GGGGGGGG-	355	-	
	IEGPTLRQCLAARA (linear)			
16	IEGPTLRQALAARA-GGGGGGGG-	356	-	
	IEGPTLRQ <u>A</u> LAARA			
17a	TMP-GGGKGGGG-TMP	357	++++	
17b	TMP-GGGK(BrAc)GGGG-TMP	358	ND	
18	TMP-GGGCGGGG-TMP	359	++++	
19	TMP-GGGK(PEG)GGGG-TMP	360	+++++	
20	TMP-GGGC(PEG)GGGG-TMP	361	+++++	
21	TMP-GGGN*GSGG-TMP	362	++++	
22	TMP-GGGCGGG-TMP	363-	~ ++++	
	TMP-GGGCGGGG-TMP	363		

<u>Discussion</u>. It is well accepted that MGDF acts in a way similar to hGH, i.e., one molecule of the protein ligand binds two molecules of the receptor for its activation. Wells <u>et al.</u>(1996), <u>Ann. Rev. Biochem.</u> 65: 609-34. Now, this interaction is mimicked by the action of a much smaller peptide, TMP. However, the present studies suggest that this mimicry requires the concerted action of two TMP molecules, as covalent dimerization of TMP in either a C-C parallel or C-N sequential fashion increased the <u>in vitro</u> biological potency of the original monomer by a factor of greater than 10³. The relatively low biopotency of the monomer is probably due to inefficient formation of the noncovalent dimer. A preformed covalent repeat has the ability to eliminate the entropy barrier for the formation of a noncovalent dimer which is exclusively driven by weak, noncovalent interactions between two molecules of the small, 14-residue peptide.

It is intriguing that this tandem repeat approach had a similar effect on enhancing bioactivity as the reported C-C dimerization is intriguing. These two strategies brought about two very different molecular configurations. The C-C dimer is a quasi-symmetrical molecule, while the tandem repeats have no such symmetry in their linear structures. Despite this difference in their primary structures, these two types of molecules appeared able to fold effectively into a similar biologically active conformation and cause the dimerization and activation of c-Mpl. These experimental observations provide a number of insights into how the two TMP molecules may interact with one another in binding to c-Mpl. First, the two C-termini of the two bound TMP molecules must be in relatively close proximity with each other, as suggested by data on the C-terminal dimer. Second, the respective N- and C-termini of the two TMP molecules in the receptor complex must also be very closely aligned with each other, such that they can be directly tethered together with a single peptide bond

to realize the near maximum activity-enhancing effect brought about by the tandem repeat strategy. Insertion of one or more (up to 14) glycine residues at the junction did not increase (or decrease) significantly the activity any further. This may be due to the fact that a flexible polyglycine peptide chain is able to loop out easily from the junction without causing any significant changes in the overall conformation. This flexibility seems to provide the freedom of orientation for the TMP peptide chains to fold into the required conformation in interacting with the receptor and validate it as a site of modification. Indirect evidence supporting this came from the study on peptide 13, in which a much more rigid b-turnforming sequence as the linker apparently forced a deviation of the backbone alignment around the linker which might have resulted in a slight distortion of the optimal conformation, thus resulting in a moderate (10-fold) decrease in activity as compared with the analogous compound with a 4-Gly linker. Third, Trp9 in TMP plays a similar role as Trp13 in EMP, which is involved not only in peptide:peptide interaction for the formation of dimers but also is important for contributing hydrophobic forces in peptide:receptor interaction. Results obtained with the W to C mutant analog, peptide 14, suggest that a covalent disulfide linkage is not sufficient to approximate the hydrophobic interactions provided by the Trp pair and that, being a short linkage, it might bring the two TMP monomers too close, therefore perturbing the overall conformation of the optimal dimeric structure.

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An analysis of the possible secondary structure of the TMP peptide can provide further understanding on the interaction between TMP and c-Mpl. This can be facilitated by making reference to the reported structure of the EPO mimetic peptide. Livnah et al. (1996), Science 273:464-75 The receptor-bound EMP has a b-hairpin structure with a b-turn formed by the highly consensus Gly-Pro-Leu-Thr at the center of its sequence. Instead of

GPLT, TMP has a highly selected GPTL sequence which is likely to form a similar turn. However, this turn-like motif is located near the N-terminal part in TMP. Secondary structure prediction using Chau-Fasman method suggests that the C-terminal half of the peptide has a tendency to adopt a helical conformation. Together with the highly conserved Trp at position 9, this C-terminal helix may contribute to the stabilization of the dimeric structure. It is interesting to note that most of our tandem repeats are more potent than the C-terminal parallel dimer. Tandem repeats seem to give the molecule a better fit conformation than does the C-C parallel dimerization. The seemingly asymmetric feature of a tandem repeat might have brought it closer to the natural ligand which, as an asymmetric molecule, uses two different sites to bind two identical receptor molecules.

Introduction of a PEG moiety was envisaged to enhance the <u>in vivo</u> activity of the modified peptide by providing it a protection against proteolytic degradation and by slowing down its clearance through renal filtration. It was unexpected that pegylation could further increase the <u>in vitro</u> bioactivity of a tandem repeated TMP peptide in the cell-based proliferation assay.

Example 2

Fc-TMP fusions

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TMPs (and EMPs as described in Example 3) were expressed in either monomeric or dimeric form as either N-terminal or C-terminal fusions to the Fc region of human IgG1. In all cases, the expression construct utilized the luxPR promoter promoter in the plasmid expression vector pAMG21.

Fc-TMP. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a monomer of the TPO-mimetic peptide was constructed using standard PCR technology. Templates for PCR reactions were the pFc-A3 vector and a synthetic TMP gene. The synthetic gene was

constructed from the 3 overlapping oligonucleotides (SEQ ID NOS: 364, 365, and 366, respectively) shown below:

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These oligonucleotides were annealed to form the duplex encoding an amino acid sequence (SEQ ID NOS: 367 and 368, respectively) shown below:

This duplex was amplified in a PCR reaction using 1842-98 and 1842-97 as the sense and antisense primers.

The Fc portion of the molecule was generated in a PCR reaction with pFc-A3 using the primers shown below (SEQ ID NOS: 369 and 370):

1216-52

AAC ATA AGT ACC TGT AGG ATC G

1830-51

TTCGATACCA CCACCTCCAC CTTTACCCGG AGACAGGGAG AGGCTCTTCTGC

The oligonucleotides 1830-51 and 1842-98 contain an overlap of 24

nucleotides, allowing the two genes to be fused together in the correct reading frame by combining the above PCR products in a third reaction using the outside primers, 1216-52 and 1842-97.

The final PCR gene product (the full length fusion gene) was digested with restriction endonucleases <u>XbaI</u> and <u>BamHI</u>, and then ligated into the vector pAMG21 and transformed into competent <u>E. coli</u> strain 2596 cells as described for EMP-Fc herein. Clones were screened for the ability to produce the recombinant protein product and to possess the

gene fusion having the correct nucleotide sequence. A single such clone was selected and designated Amgen strain #3728.

The nucleotide and amino acid sequences (SEQ ID NOS: 5 and 6) of the fusion protein are shown in Figure 7.

<u>Fc-TMP-TMP</u>. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a dimer of the TPO-mimetic peptide was constructed using standard PCR technology. Templates for PCR reactions were the pFc-A3 vector and a synthetic TMP-TMP gene. The synthetic gene was constructed from the 4 overlapping oligonucleotides (SEQ ID

NOS: 371 to 374, respectively) shown below:

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1830-52

AAA GGT GGA GGT GGT GGT GGT GGT GGT CCG
ACT CTG CGT CAG TGG CTG GCT GCT CGT GCT

1830-53

ACC TCC ACC ACC AGC AGC AGC AGC AGC CAG
CCA CTG ACG CAG AGT CGG ACC

1830-54

GGT GGT GGA GGT GGC GGC GGC GGA GGT ATT GAG GGC CCA ACC
CTT CGC CAA TGG CTT GCA GCA CGC GCA

1830-55

AAA AAA AGG ATC CTC GAG ATT ATG CGC GTG CTG CAA GCC
ATT GGC GAA GGG TTG GGC CCT CAA TAC CTC CGC CGC C
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The 4 oligonucleotides were annealed to form the duplex encoding an amino acid sequence (SEQ ID NOS: 375 and 376, respectively) shown below:

This duplex was amplified in a PCR reaction using 1830-52 and 1830-55 as the sense and antisense primers.

The Fc portion of the molecule was generated in a PCR reaction with pFc-A3 using the primers 1216-52 and 1830-51 as described above for

Fc-TMP. The full length fusion gene was obtained from a third PCR reaction using the outside primers 1216-52 and 1830-55.

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The final PCR gene product (the full length fusion gene) was digested with restriction endonucleases XbaI and BamHI, and then ligated into the vector pAMG21 and transformed into competent E. coli strain 2596 cells as described in example 1. Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected and designated Amgen strain #3727.

The nucleotide and amino acid sequences (SEQ ID NOS: 7 and 8) of the fusion protein are shown in Figure 8.

TMP-TMP-Fc. A DNA sequence coding for a tandem repeat of the TPO-mimetic peptide fused in-frame to the Fc region of human IgG1 was constructed using standard PCR technology. Templates for PCR reactions were the EMP-Fc plasmid from strain #3688 (see Example 3) and a synthetic gene encoding the TMP dimer. The synthetic gene for the tandem repeat was constructed from the 7 overlapping oligonucleotides shown below (SEQ ID NOS: 377 to 383, respectively):

20	1885-52	TTT	TTT	CAT	ATG	ATC	GAA	GGT	CCG	ACT	CTG	CGT	CAG	TGG
	1885-53		ACG CAT		AGC	CAG	CCA	CTG	ACG	CAG	AGT	CGG	ACC	TTC
25	1885-54		GCT ACA	GCT	CGT	GCT	GGT	GGA	GGC	GGT	GGG	GAC	AAA	ACT
30	1885-55		GCT GAG			GCT	GGC	GGT	GGT	GGC	GGA	GGG	GGT	GGC
	1885-56		CCA GCC				GGT	TGG	GCC	CTC	AAT	GCC	ACC	ccc
35	1885-57		CTT GGG				CTT	GCA	GCA	CGC	GCA	GGG	GGA	GGC
	1885-58	ccc	ACC	GCC	TCC	ccc	TGC	GCG	TGC	TGC				

These oligonucleotides were annealed to form the duplex shown encoding an amino acid sequence shown below (SEQ ID NOS 384 and 385):

M I E G P T L R Q W L A A R A G G 5 CCACCGCCTCCCCACCGTAACTCCCGGGTTGGGAAGCGGTTACCGAACGTCGTGCGCGT G G G G G F E G P T L R Q W L A A R A 10 GGTGGAGGCGGTGGGGACAAAACTCTGGCTGCTGGTGGTGGAGGCGGTGGGGACAAA CCCCTCCGCCACCC G G G G D K T L A A R A G G G G D K 15 ACTCACACA 181 ----- 189 THT 20

This duplex was amplified in a PCR reaction using 1885-52 and 1885-58 as the sense and antisense primers.

The Fc portion of the molecule was generated in a PCR reaction with DNA from the EMP-Fc fusion strain #3688 (see Example 3) using the primers 1885-54 and 1200-54. The full length fusion gene was obtained from a third PCR reaction using the outside primers 1885-52 and 1200-54.

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The final PCR gene product (the full length fusion gene) was digested with restriction endonucleases <u>Xba</u>I and <u>Bam</u>HI, and then ligated into the vector pAMG21 and transformed into competent <u>E. coli</u> strain 2596 cells as described for Fc-EMP herein. Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected and designated Amgen strain #3798.

The nucelotide and amino acid sequences (SEQ ID NOS: 9 and 10) of the fusion protein are shown in Figure 9.

TMP-Fc. A DNA sequence coding for a monomer of the TPO-mimetic peptide fused in-frame to the Fc region of human IgG1 was obtained fortuitously in the ligation in TMP-TMP-Fc, presumably due to the ability of primer 1885-54 to anneal to 1885-53 as well as to 1885-58. A single clone having the correct nucleotide sequence for the TMP-Fc construct was selected and designated Amgen strain #3788.

The nucleotide and amino acid sequences (SEQ ID NOS: 11 and 12) of the fusion protein are shown in Figure 10.

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Expression in E. coli. Cultures of each of the pAMG21-Fc-fusion constructs in E. coli GM221 were grown at 37 °C in Luria Broth medium containing 50 mg/ml kanamycin. Induction of gene product expression from the luxPR promoter was achieved following the addition of the synthetic autoinducer N-(3-oxohexanoyl)-DL-homoserine lactone to the culture media to a final concentration of 20 ng/ml. Cultures were incubated at 37 °C for a further 3 hours. After 3 hours, the bacterial cultures were examined by microscopy for the presence of inclusion bodies and were then collected by centrifugation. Refractile inclusion bodies were observed in induced cultures indicating that the Fc-fusions were most likely produced in the insoluble fraction in E. coli. Cell pellets were lysed directly by resuspension in Laemmli sample buffer containing 10% b-mercaptoethanol and were analyzed by SDS-PAGE. In each case, an intense coomassie-stained band of the appropriate molecular weight was observed on an SDS-PAGE gel.

pAMG21. The expression plasmid pAMG21 can be derived from the Amgen expression vector pCFM1656 (ATCC #69576) which in turn be derived from the Amgen expression vector system described in US Patent No. 4,710,473. The pCFM1656 plasmid can be derived from the described pCFM836 plasmid (Patent No. 4,710,473) by:

- (a) destroying the two endogenous <u>NdeI</u> restriction sites by end filling with T4 polymerase enzyme followed by blunt end ligation;
- (b) replacing the DNA sequence between the unique <u>AatII</u> and <u>ClaI</u> restriction sites containing the synthetic P_L promoter with a similar fragment obtained from pCFM636 (patent No. 4,710,473) containing the PL promoter (see SEQ ID NO: 386 below); and

(c) substituting the small DNA sequence between the unique <u>ClaI</u> and <u>KpnI</u> restriction sites with the oligonucleotide having the sequence of SEQ ID NO: 388.

SEQ ID NO: 386:

- The expression plasmid pAMG21 can then be derived from pCFM1656 by making a series of site-directed base changes by PCR overlapping oligo mutagenesis and DNA sequence substitutions. Starting with the BglII site (plasmid bp # 180) immediately 5' to the plasmid replication promoter

<u>Kpn</u>I

P_{COPB} and proceeding toward the plasmid replication genes, the base pair changes are as shown in Table B below.

Table B—Base pair changes resulting in pAMG21

	pAMG21 bp #	bp in pCFM1656	bp changed to in pAMG21
5	# 204	T/A	C/G
	# 428	A/T	G/C
	# 509	G/C	A/T
	# 617		insert two G/C bp
	# 679	G/C	T/A
10	# 980	T/A	C/G
	# 994	G/C	A/T
	# 1004	A/T	C/G
	# 1007	C/G	T/A
	# 1028	A/T	T/A
15	# 1047	C/G	T/A
	# 1178	G/C	T/A
	# 1466	G/C	· T/A
	# 2028	G/C	bp deletion
	# 2187	C/G	T/A
20	# 2480	A/T	T/A
	# 2499-2502	AGTG	GTCA
		TCAC	CAGT
25	# 2642	TCCGAGC AGGCTCG	7 bp deletion
	# 3435	G/C	A/T
	# 3446	G/C	A/T
30	# 3643	A/T	T/A

The DNA sequence between the unique <u>Aat</u>II (position #4364 in pCFM1656) and <u>Sac</u>II (position #4585 in pCFM1656) restriction sites is substituted with the DNA sequence (SEQ ID NO: 23) shown in Figures 17A and 17B. During the ligation of the sticky ends of this substitution DNA sequence, the outside <u>Aat</u>II and <u>Sac</u>II sites are destroyed. There are unique <u>Aat</u>II and <u>Sac</u>II sites in the substituted DNA.

GM221 (Amgen #2596). The Amgen host strain #2596 is an E.coli K-12 strain derived from Amgen strain #393. It has been modified to contain both the temperature sensitive lambda repressor cI857s7 in the early ebg region and the lacl^Q repressor in the late ebg region (68 minutes). The presence of these two repressor genes allows the use of this host with a variety of expression systems, however both of these repressors are irrelevant to the expression from $luxP_R$. The untransformed host has no antibiotic resistances.

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The ribosome binding site of the cI857s7 gene has been modified to include an enhanced RBS. It has been inserted into the <u>ebg</u> operon between nucleotide position 1170 and 1411 as numbered in Genbank accession number M64441Gb_Ba with deletion of the intervening <u>ebg</u> sequence. The sequence of the insert is shown below with lower case letters representing the <u>ebg</u> sequences flanking the insert shown below (SEQ ID NO: 388):

The construct was delivered to the chromosome using a recombinant phage called MMebg-cI857s7enhanced RBS #4 into F'tet/393.

After recombination and resolution only the chromosomal insert described

above remains in the cell. It was renamed F'tet/GM101. F'tet/GM101 was then modified by the delivery of a lacI^Q construct into the <u>ebg</u> operon between nucleotide position 2493 and 2937 as numbered in the Genbank accession number M64441Gb_Ba with the deletion of the intervening <u>ebg</u> sequence. The sequence of the insert is shown below with the lower case letters representing the <u>ebg</u> sequences flanking the insert (SEQ ID NO: 389) shown below:

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ggcggaaaccGACGTCCATCGAATGGTGCAAAACCTTTCGCGGTATGGCATGATAGCGCCCCGGAAGAGAGTCA ATTCAGGGTGGTGAATGTGAAACCAGTAACGTTATACGATGTCGCAGAGTATGCCGGTGTCTCTTATCAGACC GTTTCCCGCGTGGTGAACCAGGCCAGCCACGTTTCTGCGAAAACGCGGGAAAAAGTCGAAGCGGCGATGGCGG 10 CTCCAGTCTGGCCCTGCACGCGCCGTCGCAAATTGTCGCGCGATTAAATCTCGCGCCGATCAACTGGGTGCC AGCGTGGTGGTGTCGATGGTAGAACGAAGCGGCGTCGAAGCCTGTAAAGCGGCGGTGCACAATCTTCTCGCGC 15 TAATGTTCCGGCGTTATTTCTTGATGTCTCTGACCAGACACCCATCAACAGTATTATTTTCTCCCATGAAGAC GGTACGCGACTGGGCGTGGAGCATCTGGTCGCATTGGGTCACCAGCAAATCGCGCTGTTAGCGGGCCCATTAA GTTCTGTCTCGGCGCGTCTGCGTCTGGCTGGCTGGCATAAATATCTCACTCGCAATCAAATTCAGCCGATAGC GGAACGGGAAGGCGACTGGAGTGCCATGTCCGGTTTTCAACAAACCATGCAAATGCTGAATGAGGGCATCGTT 20 GCGTTGGTGCGGATATCTCGGTAGTGGGATACGACGATACCGAAGACAGCTCATGTTATATCCCGCCGTTAAC CACCATCAAACAGGATTTTCGCCTGCTGGGGCAAACCAGCGTGGACCGCTTGCTGCAACTCTCTCAGGGCCAG GCGGTGAAGGGCAATCAGCTGTTGCCCGTCTCACTGGTGAAAAGAAAAACCACCCTGGCGCCCCAATACGCAAA $\verb|CCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAGCTGGCACGACAGGTTTCCCGACTGGAAAGCGGACA|\\$ GTAAGGTACCATAGGATCCaggcacagga 25

The construct was delivered to the chromosome using a recombinant phage called AGebg-LacIQ#5 into F'tet/GM101. After recombination and resolution only the chromosomal insert described above remains in the cell. It was renamed F'tet/GM221. The F'tet episome was cured from the strain using acridine orange at a concentration of 25 μ g/ml in LB. The cured strain was identified as tetracyline sensitive and was stored as GM221.

Expression. Cultures of pAMG21-Fc-TMP-TMP in *E. coli* GM221 in Luria Broth medium containing 50 μg/ml kanamycin were incubated at 37°C prior to induction. Induction of Fc-TMP-TMP gene product expression from the luxPR promoter was achieved following the addition of the synthetic autoinducer N-(3-oxohexanoyl)-DL-homoserine lactone to the culture media to a final concentration of 20 ng/ml and cultures were incubated at 37°C for a further 3 hours. After 3 hours, the bacterial

cultures were examined by microscopy for the presence of inclusion bodies and were then collected by centrifugation. Refractile inclusion bodies were observed in induced cultures indicating that the Fc-TMP-TMP was most likely produced in the insoluble fraction in *E. coli*. Cell pellets were lysed directly by resuspension in Laemmli sample buffer containing 10% •-mercaptoethanol and were analyzed by SDS-PAGE. An intense Coomassie stained band of approximately 30kDa was observed on an SDS-PAGE gel. The expected gene product would be 269 amino acids in length and have an expected molecular weight of about 29.5 kDa.

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Fermentation was also carried out under standard batch conditions at the 10 L scale, resulting in similar expression levels of the Fc-TMP-TMP to those obtained at bench scale.

Purification of Fc-TMP-TMP. Cells are broken in water (1/10) by high pressure homogenization (2 passes at 14,000 PSI) and inclusion bodies are harvested by centrifugation (4200 RPM in J-6B for 1 hour). Inclusion bodies are solubilized in 6M guanidine, 50mM Tris, 8mM DTT, pH 8.7 for 1 hour at a 1/10 ratio. The solubilized mixture is diluted 20 times into 2M urea, 50 mM tris, 160mM arginine, 3mM cysteine, pH 8.5. The mixture is stirred overnight in the cold and then concentrated about 10 fold by ultafiltration. It is then diluted 3 fold with 10mM Tris, 1.5M urea, pH 9. The pH of this mixture is then adjusted to pH 5 with acetic acid. The precipitate is removed by centrifugation and the supernatant is loaded onto a SP-Sepharose Fast Flow column equilibrated in 20mM NaAc, 100 mM NaCl, pH 5(10mg/ml protein load, room temperature). The protein is eluted off using a 20 column volume gradient in the same buffer ranging from 100mM NaCl to 500mM NaCl. The pool from the column is diluted 3 fold and loaded onto a SP-Sepharose HP column in 20 mM NaAc, 150 mM NaCl, pH 5(10 mg/ml protein load, room temperature). The protein is eluted off using a 20 column volume gradient

in the same buffer ranging from 150 mM NaCl to 400 mM NaCl. The peak is pooled and filtered.

<u>Characterization of Fc-TMP activity</u>. The following is a summary of <u>in vivo</u> data in mice with various compounds of this invention.

Mice: Normal female BDF1 approximately 10-12 weeks of age.

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Bleed schedule: Ten mice per group treated on day 0, two groups started 4 days apart for a total of 20 mice per group. Five mice bled at each time point, mice were bled a minimum of three times a week. Mice were anesthetized with isoflurane and a total volume of 140-160 µl of blood was obtained by puncture of the orbital sinus. Blood was counted on a Technicon H1E blood analyzer running software for murine blood. Parameters measured were white blood cells, red blood cells, hematocrit, hemoglobin, platelets, neutrophils.

Treatments: Mice were either injected subcutaneously for a bolus treatment or implanted with 7-day micro-osmotic pumps for continuous delivery. Subcutaneous injections were delivered in a volume of 0.2 ml. Osmotic pumps were inserted into a subcutaneous incision made in the skin between the scapulae of anesthetized mice. Compounds were diluted in PBS with 0.1% BSA. All experiments included one control group, labeled "carrier" that were treated with this diluent only. The concentration of the test articles in the pumps was adjusted so that the calibrated flow rate from the pumps gave the treatment levels indicated in the graphs.

Compounds: A dose titration of the compound was delivered to mice in 7 day micro-osmotic pumps. Mice were treated with various compounds at a single dose of 100 µg/kg in 7 day osmotic pumps. Some of the same compounds were then given to mice as a single bolus injection.

Activity test results: The results of the activity experiments are shown in Figures 11 and 12. In dose response assays using 7-day micro-

osmotic pumps, the maximum effect was seen with the compound of SEQ ID NO: 18 was at 100 $\mu g/kg/day$; the 10 $\mu g/kg/day$ dose was about 50% maximally active and 1 $\mu g/kg/day$ was the lowest dose at which activity could be seen in this assay system. The compound at 10 $\mu g/kg/day$ dose was about equally active as 100 $\mu g/kg/day$ unpegylated rHu-MGDF in the same experiment.

Example 3

Fc-EMP fusions

Fc-EMP. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a monomer of the EPO-mimetic peptide was constructed using standard PCR technology. Templates for PCR reactions were a vector containing the Fc sequence (pFc-A3, described in International application WO 97/23614, published July 3, 1997) and a synthetic gene encoding EPO monomer. The synthetic gene for the monomer was constructed from the 4 overlapping oligonucleotides (SEQ ID NOS: 390 to 393, respectively) shown below:

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1798-2 TAT GAA AGG TGG AGG TGG TGG TGG TGG AGG TAC TTA CTC TTG
CCA CTT CGG CCC GCT GAC TTG G

1798-3 CGG TTT GCA AAC CCA AGT CAG CGG GCC GAA GTG GCA AGA
GTA AGT ACC TCC ACC ACC TCC ACC TTT CAT

1798-4 GTT TGC AAA CCG CAG GGT GGC GGC GGC GGC GGC GGT GGT
ACC TAT TCC TGT CAT TTT

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1798-5 CCA GGT CAG CGG GCC AAA ATG ACA GGA ATA GGT ACC ACC
GCC GCC GCC GCC ACC CTG
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The 4 oligonucleotides were annealed to form the duplex encoding an amino acid sequence (SEQ ID NOS: 394 and 395, respectively) shown below:

This duplex was amplified in a PCR reaction using

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40 1798-18 GCA GAA GAG CCT CTC CCT GTC TCC GGG TAA AGG TGG AGG TGG TGG AGG TAC TTA CTC T
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and

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1798-19
CTA ATT GGA TCC ACG AGA TTA ACC ACC
CTG CGG TTT GCA A

as the sense and antisense primers (SEQ ID NOS: 396 and 397, respectively).

The Fc portion of the molecule was generated in a PCR reaction with pFc-A3 using the primers

1216-52 AAC ATA AGT ACC TGT AGG ATC G

1798-17 AGA GTA AGT ACC TCC ACC ACC TCC ACC TTT ACC CGG
AGA CAG GGA GAG GCT CTT CTG C

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which are SEQ ID NOS: 398 and 399, respectively. The oligonucleotides 1798-17 and 1798-18 contain an overlap of 61 nucleotides, allowing the two genes to be fused together in the correct reading frame by combining the above PCR products in a third reaction using the outside primers, 1216-52 and 1798-19.

The final PCR gene product (the full length fusion gene) was digested with restriction endonucleases XbaI and BamHI, and then ligated into the vector pAMG21 (described below), also digested with XbaI and BamHI. Ligated DNA was transformed into competent host cells of E. coli strain 2596 (GM221, described herein). Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected and designated Amgen strain #3718.

The nucleotide and amino acid sequence of the resulting fusion protein (SEQ ID NOS: 15 and 16) are shown in Figure 13.

EMP-Fc. A DNA sequence coding for a monomer of the EPOmimetic peptide fused in-frame to the Fc region of human IgG1 was constructed using standard PCR technology. Templates for PCR reactions were the pFC-A3a vector and a synthetic gene encoding EPO monomer.

The synthetic gene for the monomer was constructed from the 4 overlapping oligonucleotides 1798-4 and 1798-5 (above) and 1798-6 and 1798-7 (SEQ ID NOS: 400 and 401, respectively) shown below:

1798-6 GGC CCG CTG ACC TGG GTA TGT AAG CCA CAA GGG GGT GGG GGA GGC GGG GGG TAA TCT CGA G 1798-7 GAT CCT CGA GAT TAC CCC CCG CCT CCC CCA CCC CCT TGT GGC TTA CAT AC The 4 oligonucleotides were annealed to form the duplex encoding an amino acid sequence (SEQ ID NOS: 402 and 403, respectively) shown 10 below: ${\tt GTTTGCAAACCGCAGGGTGGCGGCGGCGGCGGCGGTGGTACCTATTCCTGTCATTTTGGC}$ GTCCCACCGCCGCCGCCGCCACCATGGATAAGGACAGTAAAACCG V C K P Q G G G G G G T Y S C H F G 15 GGCGACTGGACCCATACATTCGGTGTTCCCCCACCCCCTCCGCCCCCATTAGAGCTCCTAG 20 PLTWVCKPQGGGGGG* This duplex was amplified in a PCR reaction using TTA TTT CAT ATG AAA GGT GGT AAC TAT TCC TGT CAT TTT 1798-21 25 and TGG ACA TGT GTG AGT TTT GTC CCC CCC GCC TCC CCC ACC 1798-22 CCC T 30 as the sense and antisense primers (SEQ ID NOS: 404 and 405, respectively). The Fc portion of the molecule was generated in a PCR reaction with pFc-A3 using the primers 35 1798-23 AGG GGG TGG GGG AGG CGG GGG GGA CAA AAC TCA CAC ATG and 40 GTT ATT GCT CAG CGG TGG CA 1200-54 which are SEQ ID NOS: 406 and 407, respectively. The oligonucleotides 1798-22 and 1798-23 contain an overlap of 43 nucleotides, allowing the two

The final PCR gene product (the full length fusion gene) was digested with restriction endonucleases XbaI and BamHI, and then ligated

genes to be fused together in the correct reading frame by combining the

above PCR products in a third reaction using the outside primers, 1787-21

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and 1200-54.

into the vector pAMG21 and transformed into competent <u>E. coli</u> strain 2596 cells as described above. Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected and designated Amgen strain #3688.

The nucleotide and amino acid sequences (SEQ ID NOS: 17 and 18) of the resulting fusion protein are shown in Figure 14.

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EMP-EMP-Fc. A DNA sequence coding for a dimer of the EPO-mimetic peptide fused in-frame to the Fc region of human IgG1 was constructed using standard PCR technology. Templates for PCR reactions were the EMP-Fc plasmid from strain #3688 above and a synthetic gene encoding the EPO dimer. The synthetic gene for the dimer was constructed from the 8 overlapping oligonucleotides (SEQ ID NOS:408 to 415, respectively) shown below:

15	1869-23		TTT AAG						GAT	TTG	AGT	TTT	AAC	TTT	
20	1869-48	TAA AA	AAG	TTA	AAA	CTC	AAA	TCT	AGA	ATC	AAA	TCG	ATA	AAA	
	1871-72		GGT TGC			TCT	TGC	CAC	TTC	GGC	CCG	CTG	ACT	TGG	
25	1871-73		CAG TTA					GCA	AGA	GTA	AGT	ACC	TCC	CAT	
30	1871-74		GGT TTT						GGT	GGT	ACC	TAT	TCC	TGT	
30	1871-75		ATG CTG						ACC	GCC	GCC	GCC	GCC	GCC	
35	1871-78		TGT ACT					GGT	GGG	GGA	GGC	GGG	GGG	GAC	
	1871-79		TTT TAC						ccc	ACC	ccc	TTG	TGG	CTT	

The 8 oligonucleotides were annealed to form the duplex encoding an amino acid sequence (SEQ ID NOS: 416 and 417, respectively) shown below:

		61				-+-			+				+		. .	-+-			+			TGGC + ACCG	120	
5	a		G	G	T T	Y	S								W		C	K	P	Q	G	G	-	
		121				-+-			+				+			-+-			+			TAAG + ATTC	180	
10	a		G	G	G	G	G	G			s					P	L	-	W	V	С	ĸ	-	
		181		ACA TGT		-+-			+				+							28				-
15	a		P	Q	G	G	G	G	G	G	G	D	K	T	Н	T	С	P	-					

This duplex was amplified in a PCR reaction using 1869-23 and 1871-79 (shown above) as the sense and antisense primers.

The Fc portion of the molecule was generated in a PCR reaction with strain 3688 DNA using the primers 1798-23 and 1200-54 (shown above).

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The oligonucleotides 1871-79 and 1798-23 contain an overlap of 31 nucleotides, allowing the two genes to be fused together in the correct reading frame by combining the above PCR products in a third reaction using the outside primers, 1869-23 and 1200-54.

The final PCR gene product (the full length fusion gene) was digested with restriction endonucleases <u>XbaI</u> and <u>BamHI</u>, and then ligated into the vector pAMG21 and transformed into competent <u>E. coli</u> strain 2596 cells as described for Fc-EMP. Clones were screened for ability to produce the recombinant protein product and possession of the gene fusion having the correct nucleotide sequence. A single such clone was selected and designated Amgen strain #3813.

The nucleotide and amino acid sequences (SEQ ID NOS: 19 and 20, respectively) of the resulting fusion protein are shown in Figure 15. There is a silent mutation at position 145 (A to G, shown in boldface) such that the final construct has a different nucleotide sequence than the oligonucleotide 1871-72 from which it was derived.

<u>Fc-EMP-EMP</u>. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a dimer of the EPO-mimetic peptide was

constructed using standard PCR technology. Templates for PCR reactions were the plasmids from strains 3688 and 3813 above.

The Fc portion of the molecule was generated in a PCR reaction with strain 3688 DNA using the primers 1216-52 and 1798-17 (shown above). The EMP dimer portion of the molecule was the product of a second PCR reaction with strain 3813 DNA using the primers 1798-18 (also shown above) and SEQ ID NO: 418, shown below:

1798-20 CTA ATT GGA TCC TCG AGA TTA ACC CCC TTG TGG CTT ACAT

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The oligonucleotides 1798-17 and 1798-18 contain an overlap of 61 nucleotides, allowing the two genes to be fused together in the correct reading frame by combining the above PCR products in a third reaction using the outside primers, 1216-52 and 1798-20.

The final PCR gene product (the full length fusion gene) was digested with restriction endonucleases <u>XbaI</u> and <u>BamHI</u>, and then ligated into the vector pAMG21 and transformed into competent <u>E. coli</u> strain 2596 cells as described for Fc-EMP. Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected and designated Amgen strain #3822.

The nucleotide and amino acid sequences (SEQ ID NOS: __ and __, respectively) of the fusion protein are shown in Figure 16.

<u>Characterization of Fc-EMP activity</u>. Characterization was carried out <u>in vivo</u> as follows.

Mice: Normal female BDF1 approximately 10-12 weeks of age.

Bleed schedule: Ten mice per group treated on day 0, two groups started 4 days apart for a total of 20 mice per group. Five mice bled at each time point, mice were bled a maximum of three times a week. Mice were anesthetized with isoflurane and a total volume of 140-160 ml of blood was obtained by puncture of the orbital sinus. Blood was counted

on a Technicon H1E blood analyzer running software for murine blood. Parameters measured were WBC, RBC, HCT, HGB, PLT, NEUT, LYMPH.

Treatments: Mice were either injected subcutaneously for a bolus treatment or implanted with 7 day micro-osmotic pumps for continuous delivery. Subcutaneous injections were delivered in a volume of 0.2 ml. Osmotic pumps were inserted into a subcutaneous incision made in the skin between the scapulae of anesthetized mice. Compounds were diluted in PBS with 0.1% BSA. All experiments included one control group, labeled "carrier" that were treated with this diluent only. The concentration of the test articles in the pumps was adjusted so that the calibrated flow rate from the pumps gave the treatment levels indicated in the graphs.

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Experiments: Various Fc-conjugated EPO mimetic peptides (EMPs) were delivered to mice as a single bolus injection at a dose of $100 \,\mu\text{g/kg}$. Fc-EMPs were delivered to mice in 7-day micro-osmotic pumps. The pumps were not replaced at the end of 7 days. Mice were bled until day 51 when HGB and HCT returned to baseline levels.

Example 4

TNF-α inhibitors

Fc-TNF-α inhibitors. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a monomer of the TNF-α inhibitory peptide was constructed using standard PCR technology. The Fc and 5 glycine linker portion of the molecule was generated in a PCR reaction with DNA from the Fc-EMP fusion strain #3718 (see Example 3) using the sense primer 1216-52 and the antisense primer 2295-89 (SEQ ID NOS: 1112 and 1113, respectively). The nucleotides encoding the TNF-α inhibitory peptide were provided by the PCR primer 2295-89 shown below:

TGC GGC AGG AAG TCA CCA CCA CCT CCA CCT TTA CCC

The oligonucleotide 2295-89 overlaps the glycine linker and Fc portion of the template by 22 nucleotides, with the PCR resulting in the two genes being fused together in the correct reading frame.

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The PCR gene product (the full length fusion gene) was digested with restriction endonucleases <u>Nde</u>I and <u>Bam</u>HI, and then ligated into the vector pAMG21 and transformed into competent <u>E. coli</u> strain 2596 cells as described for EMP-Fc herein. Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected and designated Amgen strain #4544.

The nucleotide and amino acid sequences (SEQ ID NOS: 1055 and 1056) of the fusion protein are shown in Figures 19A and 19B.

TNF-α inhibitor-Fc. A DNA sequence coding for a TNF-α inhibitory peptide fused in-frame to the Fc region of human IgG1 was constructed using standard PCR technology. The template for the PCR reaction was a plasmid containing an unrelated peptide fused via a five glycine linker to Fc. The nucleotides encoding the TNF-α inhibitory peptide were provided by the sense PCR primer 2295-88, with primer 1200-54 serving as the antisense primer (SEQ ID NOS: 1117 and 407, respectively). The primer sequences are shown below:

2295-88 GAA TAA CAT ATG GAC TTC CTG CCG CAC TAC AAA AAC ACC TCT CTG GGT CAC CGT CCG GGT GGA GGC GGT GGG GAC AAA ACT

1200-54 GTT ATT GCT CAG CGG TGG CA

The oligonucleotide 2295-88 overlaps the glycine linker and Fc portion of the template by 24 nucleotides, with the PCR resulting in the two genes being fused together in the correct reading frame.

The PCR gene product (the full length fusion gene) was digested with restriction endonucleases <u>Nde</u>I and <u>Bam</u>HI, and then ligated into the vector pAMG21 and transformed into competent <u>E. coli</u> strain 2596 cells as described for EMP-Fc herein. Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected and designated Amgen strain #4543.

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The nucleotide and amino acid sequences (SEQ ID NOS: 1057 and 1058) of the fusion protein are shown in Figures 20A and 20B.

Expression in E. coli. Cultures of each of the pAMG21-Fc-fusion constructs in E. coli GM221 were grown at 37 °C in Luria Broth medium containing 50 mg/ml kanamycin. Induction of gene product expression from the luxPR promoter was achieved following the addition of the synthetic autoinducer N-(3-oxohexanoyl)-DL-homoserine lactone to the culture media to a final concentration of 20 ng/ml. Cultures were incubated at 37 °C for a further 3 hours. After 3 hours, the bacterial cultures were examined by microscopy for the presence of inclusion bodies and were then collected by centrifugation. Refractile inclusion bodies were observed in induced cultures indicating that the Fc-fusions were most likely produced in the insoluble fraction in E. coli. Cell pellets were lysed directly by resuspension in Laemmli sample buffer containing 10% β -mercaptoethanol and were analyzed by SDS-PAGE. In each case, an intense coomassie-stained band of the appropriate molecular weight was observed on an SDS-PAGE gel.

Purification of Fc-peptide fusion proteins. Cells are broken in water (1/10) by high pressure homogenization (2 passes at 14,000 PSI) and inclusion bodies are harvested by centrifugation (4200 RPM in J-6B for 1 hour). Inclusion bodies are solubilized in 6M guanidine, 50mM Tris, 8mM DTT, pH 8.7 for 1 hour at a 1/10 ratio. The solubilized mixture is diluted

20 times into 2M urea, 50 mM tris, 160mM arginine, 3mM cysteine, pH 8.5. The mixture is stirred overnight in the cold and then concentrated about 10 fold by ultafiltration. It is then diluted 3 fold with 10mM Tris, 1.5M urea, pH 9. The pH of this mixture is then adjusted to pH 5 with acetic acid. The precipitate is removed by centrifugation and the supernatant is loaded onto a SP-Sepharose Fast Flow column equilibrated in 20mM NaAc, 100 mM NaCl, pH 5 (10mg/ml protein load, room temperature). The protein is eluted from the column using a 20 column volume gradient in the same buffer ranging from 100mM NaCl to 500mM NaCl. The pool from the column is diluted 3 fold and loaded onto a SP-Sepharose HP column in 20mM NaAc, 150mM NaCl, pH 5(10mg/ml protein load, room temperature). The protein is eluted using a 20 column volume gradient in the same buffer ranging from 150mM NaCl to 400mM NaCl. The peak is pooled and filtered.

<u>Characterization of activity of Fc-TNF- α inhibitor and TNF- α inhibitor -Fc. Binding of these peptide fusion proteins to TNF- α can be characterized by BIAcore by methods available to one of ordinary skill in the art who is armed with the teachings of the present specification.</u>

Example 5

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IL-1 Antagonists

Fc-IL-1 antagonist. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a monomer of an IL-1 antagonist peptide was constructed using standard PCR technology. The Fc and 5 glycine linker portion of the molecule was generated in a PCR reaction with DNA from the Fc-EMP fusion strain #3718 (see Example 3) using the sense primer 1216-52 and the antisense primer 2269-70 (SEQ ID NOS: 1112 and 1118, respectively). The nucleotides encoding the IL-1 antagonist peptide were provided by the PCR primer 2269-70 shown below:

1216-52	AAC A	ATA AG	T ACC	TGT	AGG	ATC	G							
2269-70	CCG C	CGG AT	C CAT T TCG	TAC AAA	AGC CCA	GGC CCA	AGA CCT	GCG CCA	TAC CCT	GGC TTA	TGC CCC	CAG	TAA	CCC

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The oligonucleotide 2269-70 overlaps the glycine linker and Fc portion of the template by 22 nucleotides, with the PCR resulting in the two genes being fused together in the correct reading frame.

The PCR gene product (the full length fusion gene) was digested with restriction endonucleases <u>Nde</u>I and <u>Bam</u>HI, and then ligated into the vector pAMG21 and transformed into competent <u>E. coli</u> strain 2596 cells as described for EMP-Fc herein. Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected and designated Amgen strain #4506.

The nucleotide and amino acid sequences (SEQ ID NOS: 1059 and 1060) of the fusion protein are shown in Figures 21A and 21B.

<u>IL-1 antagonist-Fc.</u> A DNA sequence coding for an IL-1 antagonist peptide fused in-frame to the Fc region of human IgG1 was constructed using standard PCR technology. The template for the PCR reaction was a plasmid containing an unrelated peptide fused via a five glycine linker to Fc. The nucleotides encoding the IL-1 antagonist peptide were provided by the sense PCR primer 2269-69, with primer 1200-54 serving as the antisense primer (SEQ ID NOS: 1119 and 407, respectively). The primer sequences are shown below:

30				CAT CTG								CAG	CCG	TAC	GCT
	1200-54	GTT	ATT	GCT	CAG	CGG	TGG	CA			•				

The oligonucleotide 2269-69 overlaps the glycine linker and Fc portion of the template by 24 nucleotides, with the PCR resulting in the two genes being fused together in the correct reading frame.

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The PCR gene product (the full length fusion gene) was digested with restriction endonucleases <u>Nde</u>I and <u>Bam</u>HI, and then ligated into the vector pAMG21 and transformed into competent <u>E. coli</u> strain 2596 cells as described for EMP-Fc herein. Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected and designated Amgen strain #4505.

The nucleotide and amino acid sequences (SEQ ID NOS: 1061 and 1062) of the fusion protein are shown in Figures 22A and 22B. Expression and purification were carried out as in previous examples.

Characterization of Fc-IL-1 antagonist peptide and IL-1 antagonist

peptide-Fc activity. IL-1 Receptor Binding competition between IL-1β, IL
1RA and Fc-conjugated IL-1 peptide sequences was carried out using the

IGEN system. Reactions contained 0.4 nM biotin-IL-1R + 15 nM IL-1-TAG

+ 3 uM competitor + 20 ug/ml streptavidin-conjugate beads, where

competitors were IL-1RA, Fc-IL-1 antagonist, IL-1 antagonist-Fc).

Competition was assayed over a range of competitor concentrations from

3 uM to 1.5 pM. The results are shown in Table C below:

Table C—Results from IL-1 Receptor Binding Competition Assay

		IL-1pep-Fc	Fc-IL-1pep	IL-1ra
5	KI EC50	281.5 530.0	59.58 112.2	1.405 2.645
	95% Confidence	Intervals		
10	EC50	280.2 to 1002	54.75 to 229.8	1.149 to 6.086
1 -	KI	148.9 to 532.5	29.08 to 122.1	0.6106 to 3.233
15	Goodness of Fit			
	R²	0.9790	0.9687	0.9602

Example 6

VEGF-Antagonists

Fc-VEGF Antagonist. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a monomer of the VEGF mimetic peptide was constructed using standard PCR technology. The templates for the PCR reaction were the pFc-A3 plasmid and a synthetic VEGF mimetic peptide gene. The synthetic gene was assembled by annealing the following two oligonucleotides primer (SEQ ID NOS: 1120 and 1121,

10 respectively):

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2293-11 GTT GAA CCG AAC TGT GAC ATC CAT GTT ATG TGG GAA TGG GAA TGT TTT GAA CGT CTG

2293-12 CAG ACG TTC AAA ACA TTC CCA TTC CCA CAT AAC ATG GAT GTC ACA GTT CGG TTC AAC

The two oligonucleotides anneal to form the following duplex encoding an amino acid sequence shown below (SEQ ID NOS 1122):

This duplex was amplified in a PCR reaction using 2293-05 and 2293-06 as the sense and antisense primers (SEQ ID NOS. 1125 and 1126).

The Fc portion of the molecule was generated in a PCR reaction with the pFc-A3 plasmid using the primers 2293-03 and 2293-04 as the sense and antisense primers (SEQ ID NOS. 1123 and 1124, respectively). The full length fusion gene was obtained from a third PCR reaction using the outside primers 2293-03 and 2293-06. These primers are shown below:

	2293-03	ATT	TGA	TTC	TAG	AAG	GAG	GAA	TAA	CAT	ATG	GAC	AAA	ACT	CAC
		ACA	TGT												
5	2293-04	GTC	ACA	GTT	CGG	TTC	AAC	ACC	ACC	ACC	ACC	ACC	TTT	ACC	CGG
		AGA	CAG	GGA											
	2293-05	TCC	CTG	TCT	CCG	GGT	AAA	GGT	GGT	GGT	GGT	GGT	GTT	GAA	CCG
		AAC	TGT	GAC	ATC					•					
10	2293-06	CCG	CGG	ATC	CTC	GAG	TTA	CAG	ACG	TTC	AAA	ACA	TTC	CCA	

The PCR gene product (the full length fusion gene) was digested with restriction endonucleases <u>Nde</u>I and <u>Bam</u>HI, and then ligated into the vector pAMG21 and transformed into competent <u>E. coli</u> strain 2596 cells as described for EMP-Fc herein. Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected and designated Amgen strain #4523.

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The nucleotide and amino acid sequences (SEQ ID NOS: 1063 and 1064) of the fusion protein are shown in Figures 23A and 23B.

<u>VEGF antagonist -Fc</u>. A DNA sequence coding for a VEGF mimetic peptide fused in-frame to the Fc region of human IgG1 was constructed using standard PCR technology. The templates for the PCR reaction were the pFc-A3 plasmid and the synthetic VEGF mimetic peptide gene described above. The synthetic duplex was amplified in a PCR reaction using 2293-07 and 2293-08 as the sense and antisense primers (SEQ ID NOS. 1127 and 1128, respectively).

The Fc portion of the molecule was generated in a PCR reaction with the pFc-A3 plasmid using the primers 2293-09 and 2293-10 as the sense and antisense primers (SEQ ID NOS. 1129 and 1130, respectively).

The full length fusion gene was obtained from a third PCR reaction using the outside primers 2293-07 and 2293-10. These primers are shown below:

	2293-07	ATT	TGA	TTC	TAG	AAG	GAG	GAA	TAA	CAT	ATG	GTT	GAA	CCG	AAC
5		TGT	GAC												
	2293-08		TGT ACA		AGT	TTT	GTC	ACC	ACC	ACC	ACC	ACC	CAG	ACG ⁻	TTC
10	2293-09		TGT ACA		GAA	CGT	СТG	GGT	GGT	GGT	GGT	GGT	GAC	AAA	ACT

The PCR gene product (the full length fusion gene) was digested with restriction endonucleases Ndel and BamHI, and then ligated into the vector pAMG21 and transformed into competent E. coli strain 2596 cells as described for EMP-Fc herein. Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected and designated Amgen strain #4524.

The nucleotide and amino acid sequences (SEQ ID NOS: 1065 and 1066) of the fusion protein are shown in Figures 24A and 24B. Expression and purification were carried out as in previous examples.

25 <u>Example 7</u>

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MMP Inhibitors

<u>Fc-MMP inhibitor</u>. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a monomer of an MMP inhibitory peptide was constructed using standard PCR technology. The Fc and 5 glycine linker portion of the molecule was generated in a PCR reaction with DNA from the Fc-TNF-α inhibitor fusion strain #4544 (see Example 4) using the sense primer 1216-52 and the antisense primer 2308-67 (SEQ ID NOS: 1112

and 1131, respectively). The nucleotides encoding the MMP inhibitor peptide were provided by the PCR primer 2308-67 shown below:

1216-52 AAC ATA AGT ACC TGT AGG ATC G

CCG CGG ATC CAT TAG CAC AGG GTG AAA CCC CAG TGG GTG CAA CCA CCA CCT CCA CCT TTA CCC

The oligonucleotide 2308-67 overlaps the glycine linker and Fc portion of the template by 22 nucleotides, with the PCR resulting in the two genes being fused together in the correct reading frame.

The PCR gene product (the full length fusion gene) was digested with restriction endonucleases <u>Nde</u>I and <u>Bam</u>HI, and then ligated into the vector pAMG21 and transformed into competent <u>E. coli</u> strain 2596 cells as described for EMP-Fc herein. Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected and designated Amgen strain #4597.

The nucleotide and amino acid sequences (SEQ ID NOS: 1067 and 1068) of the fusion protein are shown in Figures 25A and 25B. Expression and purification were carried out as in previous examples.

MMP Inhibitor-Fc. A DNA sequence coding for an MMP inhibitory peptide fused in-frame to the Fc region of human IgG1 was constructed using standard PCR technology. The Fc and 5 glycine linker portion of the molecule was generated in a PCR reaction with DNA from the Fc-TNF- α inhibitor fusion strain #4543 (see Example 4). The nucleotides encoding the MMP inhibitory peptide were provided by the sense PCR primer 2308-66, with primer 1200-54 serving as the antisense primer (SEQ ID NOS: 1132 and 407, respectively). The primer sequences are shown below:

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2308-66 GAA TAA CAT ATG TGC ACC CAC TGG GGT TTC ACC CTG TGC GGT GGA GGC GGT GGG GAC AAA

35 1200-54 GTT ATT GCT CAG CGG TGG CA

The oligonucleotide 2269-69 overlaps the glycine linker and Fc portion of the template by 24 nucleotides, with the PCR resulting in the two genes being fused together in the correct reading frame.

The PCR gene product (the full length fusion gene) was digested with restriction endonucleases Ndel and BamHI, and then ligated into the vector pAMG21 and transformed into competent E. coli strain 2596 cells as described for EMP-Fc herein. Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected and designated Amgen strain #4598.

The nucleotide and amino acid sequences (SEQ ID NOS: 1069 and 1070) of the fusion protein are shown in Figures 26A and 26B.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto, without departing from the spirit and scope of the invention as set forth herein.

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Abbreviations

Abbreviations used throughout this specification are as defined below, unless otherwise defined in specific circumstances.

	Ac	acetyl (used to refer to acetylated residues)
	AcBpa	acetylated p-benzoyl-L-phenylalanine
25	ADCC	antibody-dependent cellular cytotoxicity
	Aib	aminoisobutyric acid
	··· bA	beta-alanine
	Вра	p-benzoyl-L-phenylalanine
	BrAc	bromoacetyl (BrCH ₂ C(O)

	BSA	Bovine serum albumin
	Bzl	Benzyl
	Cap	Caproic acid
	CTL	Cytotoxic T lymphocytes
5	CTLA4	Cytotoxic T lymphocyte antigen 4
	DARC	Duffy blood group antigen receptor
	DCC	Dicylcohexylcarbodiimide
	Dde	1-(4,4-dimethyl-2,6-dioxo-cyclohexylidene)ethyl
	EMP	Erythropoietin-mimetic peptide
10	ESI-MS	Electron spray ionization mass spectrometry
	EPO	Erythropoietin
	Fmoc	fluorenylmethoxycarbonyl
	G-CSF	Granulocyte colony stimulating factor
	GH	Growth hormone
15	HCT	hematocrit
	HGB	hemoglobin
	hGH	Human growth hormone
	HOBt	1-Hydroxybenzotriazole
	HPLC	high performance liquid chromatography
20	IL	interleukin
	IL-R	interleukin receptor
	IL-1R	interleukin-1 receptor
	IL-1ra	interleukin-1 receptor antagonist
	Lau	Lauric acid
25	LPS	lipopolysaccharide
	LYMPH	lymphocytes
	MALDI-MS	Matrix-assisted laser desorption ionization mass
		spectrometry
	Me	methyl

	MeO	methoxy
	MHC	major histocompatibility complex
	MMP	matrix metalloproteinase
	MMPI	matrix metalloproteinase inhibitor
5	1-Nap	1-napthylalanine
	NEUT	neutrophils
	NGF	nerve growth factor
	Nle	norleucine
	NMP	N-methyl-2-pyrrolidinone
10	PAGE	polyacrylamide gel electrophoresis
	PBS	Phosphate-buffered saline
	Pbf	2,2,4,6,7-pendamethyldihydrobenzofuran-5-sulfonyl
	PCR	polymerase chain reaction
	Pec	pipecolic acid
15	PEG	Poly(ethylene glycol)
	pGlu	pyroglutamic acid
	Pic	picolinic acid
	PLT	platelets
	pΥ	phosphotyrosine
20	RBC	red blood cells
	RBS	ribosome binding site
	RT	room temperature (25 °C)
	Sar	sarcosine
	SDS	sodium dodecyl sulfate
25	STK	serine-threonine kinases
	t-Boc	tert-Butoxycarbonyl
	··· tBu	tert-Butyl
	TGF	tissue growth factor
	THF	thymic humoral factor

ΤK tyrosine kinase **TMP** Thrombopoietin-mimetic peptide Tissue necrosis factor **TNF** TPO Thrombopoietin TNF-related apoptosis-inducing ligand 5 **TRAIL** Trt trityl UK urokinase urokinase receptor UKR vascular endothelial cell growth factor **VEGF** VIP vasoactive intestinal peptide 10 **WBC** white blood cells

What is claimed is:

1. A composition of matter of the formula

$$(X^1)_a - F^1 - (X^2)_b$$

and multimers thereof, wherein:

5 F¹ is an Fc domain;

 X^{1} and X^{2} are each independently selected from - $(L^{1})_{c}$ - P^{1} , - $(L^{1})_{c}$ - P^{1} - $(L^{2})_{d}$ - P^{2} - $(L^{2})_{d}$ - P^{2} - $(L^{3})_{e}$ - P^{3} , and - $(L^{1})_{c}$ - P^{1} - $(L^{2})_{d}$ - P^{2} - $(L^{3})_{e}$ - P^{3} - $(L^{4})_{c}$ - P^{4}

P¹, P², P³, and P⁴ are each independently sequences of pharmacologically active peptides;

L¹, L², L³, and L⁴ are each independently linkers; and a, b, c, d, e, and f are each independently 0 or 1, provided that at least one of a and b is 1.

2. The composition of matter of Claim 1 of the formulae

15 X¹-F¹

or

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 F^1-X^2

3. The composition of matter of Claim 1 of the formula $F^1-(L^1)_-P^1$.

- 20 4. The composition of matter of Claim 1 of the formula $F^{1}-(L^{1})_{c}-P^{1}-(L^{2})_{d}-P^{2}.$
 - 5. The composition of matter of Claim 1 wherein F¹ is an IgG Fc domain.
- 6. The composition of matter of Claim 1 wherein F¹ is an IgG1 Fc domain.
 - 7. The composition of matter of Claim 1 wherein F¹ comprises the sequence of SEQ ID NO: 2.
 - 8. The composition of matter of Claim 1 wherein X¹ and X² comprise an IL-1 antagonist peptide sequence.

9. The composition of matter of Claim 8 wherein the IL-1 antagonist peptide sequence is selected from SEQ ID NOS: 212, 907, 908, 909, 910, 917, and 979.

10. The composition of matter of Claim 8 wherein the IL-1 antagonist peptide sequence is selected from SEQ ID NOS: 213 to 271, 671 to 906, 911 to 916, and 918 to 1023.

- 11. The composition of matter of Claim 8 wherein F¹ comprises the sequence of SEQ ID NO: 2.
- The composition of matter of Claim 1 wherein X¹ and X² comprise
 an EPO-mimetic peptide sequence.
 - 13. The composition of matter of Claim 12 wherein the EPO-mimetic peptide sequence is selected from Table 5.
 - 14. The composition of matter of Claim 12 wherein F¹ comprises the sequence of SEQ ID NO: 2.
- 15. The composition of matter of Claim 12 comprising a sequence selected from SEQ ID NOS: 83, 84, 85, 124, 419, 420, 421, and 461.
 - 16. The composition of matter of claim 12 comprising a sequence selected from SEQ ID NOS: 339 and 340.
- 17. The composition of matter of Claim 12 comprising a sequence20 selected from SEQ ID NOS: 20 and 22.
 - 18. The composition of matter of Claim 3 wherein P¹ is a TPO-mimetic peptide sequence.
 - 19. The composition of matter of Claim 18 wherein P¹ is a TPO-mimetic peptide sequence selected from Table 6.
- 25 20. The composition of matter of Claim 18 wherein F¹ comprises the sequence of SEQ ID NO: 2.
 - 21. The composition of matter of Claim 18 having a sequence selected from SEQ ID NOS: 6 and 12.
 - 22. A DNA encoding a composition of matter of any of Claims 1 to 21.

- 23. An expression vector comprising the DNA of Claim 22.
- 24. A host cell comprising the expression vector of Claim 23.
- 25. The cell of Claim 24, wherein the cell is an <u>E. coli</u> cell.

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- 26. A process for preparing a pharmacologically active compound, which comprises
 - selecting at least one randomized peptide that modulates the
 activity of a protein of interest; and
 - b) preparing a pharmacologic agent comprising at least one Fc domain covalently linked to at least one amino acid sequence of the selected peptide or peptides.
- 27. The process of Claim 26, wherein the peptide is selected in a process comprising screening of a phage display library, an <u>E. coli</u> display library, a ribosomal library, or a chemical peptide library.
- 28. The process of Claim 26, wherein the preparation of the pharmacologic agent is carried out by:
 - a) preparing a gene construct comprising a nucleic acid
 sequence encoding the selected peptide and a nucleic acid
 sequence encoding an Fc domain; and
 - b) expressing the gene construct.
- 20 29. The process of Claim 26, wherein the gene construct is expressed in an <u>E. coli</u> cell.
 - 30. The process of Claim 26, wherein the protein of interest is a cell surface receptor.
- 31. The process of Claim 26, wherein the protein of interest has a linear epitope.
 - 32. The process of Claim 26, wherein the protein of interest is a cytokine receptor.
 - 33. The process of Claim 26, wherein the peptide is an EPO-mimetic peptide.

34. The process of Claim 26, wherein the peptide is a TPO-mimetic peptide.

- 35. The process of Claim 26, wherein the peptide is an IL-1 antagonist peptide.
- 5 36. The process of Claim 26, wherein the peptide is an MMP inhibitor peptide or a VEGF antagonist peptide.
 - 37. The process of Claim 26, wherein the peptide is a TNF-antagonist peptide.
- 38. The process of Claim 26, wherein the peptide is a CTLA4-mimetic peptide.
 - 39. The process of Claim 26, wherein the peptide is selected from Tables 4 to 20.
 - 40. The process of Claim 26, wherein the selection of the peptide is carried out by a process comprising:

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- a) preparing a gene construct comprising a nucleic acid
 sequence encoding a first selected peptide and a nucleic acid
 sequence encoding an Fc domain;
 - b) conducting a polymerase chain reaction using the gene construct and mutagenic primers, wherein
 - i) a first mutagenic primer comprises a nucleic acid
 sequence complementary to a sequence at or near the
 5' end of a coding strand of the gene construct, and
 - ii) a second mutagenic primer comprises a nucleic acid sequence complementary to the 3' end of the noncoding strand of the gene construct.
- 41. The process of Claim 26, wherein the compound is derivatized.
- 42. The process of Claim 26, wherein the derivatized compound comprises a cyclic portion, a cross-linking site, a non-peptidyl

linkage, an N-terminal replacement, a C-terminal replacement, or a modified amino acid moiety.

- 43. The process of Claim 26 wherein the Fc domain is an IgG Fc domain.
- 5 44. The process of Claim 26, wherein the vehicle is an IgG1 Fc domain.
 - 45. The process of Claim 26, wherein the vehicle comprises the sequence of SEQ ID NO: 2.
 - 46. The process of Claim 26, wherein the compound prepared is of the formula

10 $(X^1)_a - F^1 - (X^2)_b$

and multimers thereof, wherein:

F¹ is an Fc domain;

 X^{1} and X^{2} are each independently selected from $-(L^{1})_{c}-P^{1}$, $-(L^{1})_{c}-P^{1}-(L^{2})_{d}-P^{2}-(L^{3})_{e}-P^{3}$, and $-(L^{1})_{c}-P^{1}-(L^{2})_{d}-P^{2}-(L^{3})_{e}-P^{3}-(L^{4})_{f}-P^{4}$

P¹, P², P³, and P⁴ are each independently sequences of pharmacologically active peptides;

 L^1 , L^2 , L^3 , and L^4 are each independently linkers; and a, b, c, d, e, and f are each independently 0 or 1, provided that at least one of a and b is 1.

47. The process of Claim 46, wherein the compound prepared is of the formulae

X¹-F¹

or

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F¹-X²

48. The process of Claim 46, wherein the compound prepared is of the formulae

or

$$F^{1}-(L^{1})_{c}-P^{1}-(L^{2})_{d}-P^{2}.$$

- 49. The process of Claim 46, wherein F¹ is an IgG Fc domain.
- 50. The process of Claim 46, wherein F¹ is an IgG1 Fc domain.
- 5 51. The process of Claim 46, wherein F¹ comprises the sequence of SEQ ID NO: 2.

FIG. 1

peptide selection

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peptide optimization

1

formation of Fc-peptide DNA construct



insertion of construct into expression vector



transfection of host cell with vector



expression of vector in host cell



Fc multimer formation in host cell

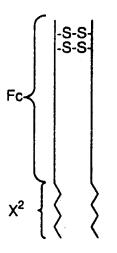


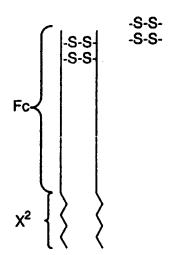
isolation of Fc multimer from host cell

FIG. 2A

FIG. 2B

FIG. 2C





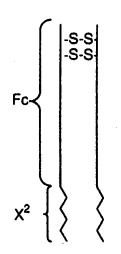
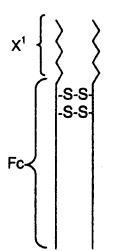
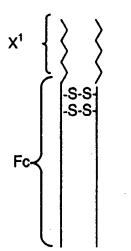


FIG. 2D FIG. 2E

FIG. 2F





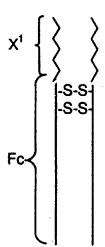


FIG. 3A

FIG. 3B

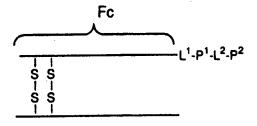


FIG. 3C

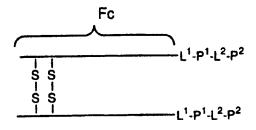
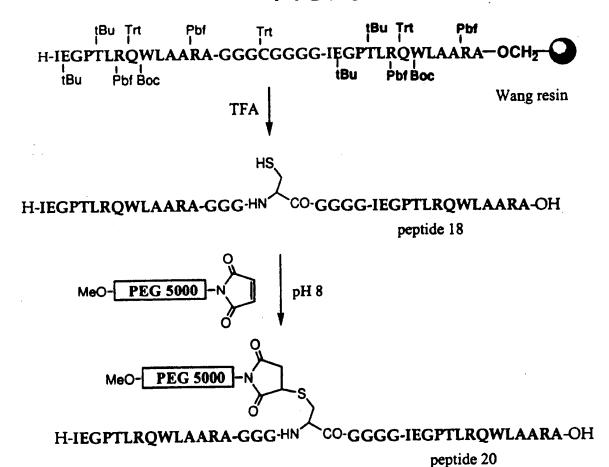


FIG. 4

	1	ATGGACAAAACTCACACATGTCCACCTTGTCCAGCTCCGGAACTCCTGGGGGGACCGTCA														٠.						
	1	TAC	CTC	3TT	rtg	AGT	GTG'	TAC								rg a c	GAC	:ccc	CCI	GGC	AGT	60
a		M	α	ĸ	T	H	T	С	P	P	С	P	A	P	E	L	L	G	G	P	S	-
	61		TTC	CT	CTTC	CCC	CCC.	AAA +	ACC	CAA	GGA(CAC	CTC	CATO	ATC	TCC	CGG	ACC	CCI	GAG	GTC	120
	0.1		SAA(GA											TAC	AGC	GCC	TGO	GGA	CTC	CAG	120
a		V	F	L	F	P	P	K	p	K	D	T	L	M	I	S	R	T	P	E	V	•
																			TGG	TAC	GTG	
	121							GCA(ACC	ATG	CAC	180
a		T .	С	V	V	v	D	v	S	н	E	D	P	E	V	K	F	N	W	Y	V	.•
	101																			-	ACG	240
	181																				TGC	240
a		D	G	v	E	v	Н	N	A	ĸ	T	K	P	R	E	Ε	Q	Y	N	S	Ť	
																					TAC	
	241																				ATG	300
a		Y.	R	v	v	s	v	L	T	v	L	Н	Q	D	W	L	N	G	K	E	Y	•
	301		STG	CAA				CAA											TCC	ÁAA	GCC	360
	301		CAC	GTT(AGG	TTT	CGG	300
a		K	С	K	V	S	N	K	A	L	P	A	P	I	E	ĸ	T	I	S	K	A	-
	361																				ACC	420
	301																				TGG	420
a		K	G	Q	P	R	E	P	Q	V	Y	T	L	P	P	S	R	D	E	L	T	•
	421		GAA(CA				GAC										GAC	ATC	GCC	GTG +	480
			TTC	GT(CTG	TAG	CGG	CAC	
a		K	N	Q	V	S	L	T	С	L	V	K	G	F	Y	P	S	D	I	A	V	•
	481																				GAC	540
																					CTG	
a								-													D	•
	541								CTA	CAG	CAA	GCT(+	CAC	CGT	GAC	AAC	AGC	AGC	TGG	CAG	CAG	600
									GAT(GTC	GTT(CGA	GTG(GCAC	CTC	TTC	TCC	HCC.	ACC	GTC	GTC	٠.
a								L														-
	601				-+-			+				+		• • • ·	-+			+ -	·		AAG	660
																					TTC	
a											H	E	A	L	H	N	H	Y	T	Q	K	-
	661				-+-					-	684											
		TC	GGA (3AG	GGA(CCC. STIT			4FF	T /	3111	E 2	6)							
						3	UD	7111	V 1 1			٠. ر.		_ ~ '	~,							

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FIG. 6



XbaI

FIG. 7

c	1	TCTAGATTTGTTTTAACTAATTAAAGGAGGAATAACATATGGACAAAACTCACACATGTC AGATCTAAACAAAATTGATTAATTTCCTCCTTATTGTATACCTGTTTTGAGTGTGTACAG M D K T H T C P	
с	61	CACCTTGTCCAGCTCCGGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAAC GTGGAACAGGTCGAGGCCTTGAGGACCCCCCTGGCAGTCAGAAGGAGAAGGGGGGGTTTTG P C P A P E L L G G P S V F L F P P K P	120
с	121	CCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGA GGTTCCTGTGGGAGTACTAGAGGGCCTGGGGACTCCAGTGTACGCACCACCACCACCACCTCACT K D T L M I S R T P E V T C V V V D V S	
c	181	GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGCGTGGAGGTGCATAATG CGGTGCTTCTGGGACTCCAGTTCAAGTTGACCATGCACCTGCCGCACCTCCACGTATTAC H E D P E V K F N W Y V D G V E V H N A	
c	241	CCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCA GGTTCTGTTTCGGCGCCCCTCCTCGTCATGTTGTCGTGCATGGCACACCAGTCGCAGGAGT K T K P R E E Q Y N S T Y R V V S V L T	
с	301	CCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAG GGCAGGACGTGGTCCTGACCGACTTACCGTTCCTCATGTTCACGTTCCAGAGGTTGTTTC V L H Q D W L N G K E Y K C K V S N K A	
c	361	CCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCAC GGGAGGGTCGGGGGTAGCTCTTTTGGTAGAGGTTTCCGGTTTCCCGTCGGGGCTCTTGGTG L P A P I E K T I S K A K G Q P R E P Q	
c	421	AGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCT TCCACATGTGGGACGGGGGTAGGGCCCTACTCGACTGGTTCTTGGTCCAGTCGGACTGGA V Y T L P P S R D E L T K N Q V S L T C	
c	481	GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGC CGGACCAGTTTCCGAAGATAGGGTCGCTGTAGCGGCACCTCACCCTCTCGTTACCCGTCG L V K G F Y P S D I A V E W E S N G Q P	
c	541	CGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCT GCCTCTTGTTGATGTTCTGGTGCGGAGGGCACGACCTGAGGCTGCCGAGGAAGAAGGAGA E N N Y K T T P P V L D S D G S F F L Y	600 -
c	601	ACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGGAACGTCTTCTCATGCTCCG TGTCGTTCGAGTGGCACCTGTTCTCGTCCACCGTCGTCCCCTTGCAGAAGAGTACGAGGC S K L T V D K S R W Q Q G N V F S C S V	
c	661	TGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTA ACTACGTACTCCGAGACGTGTTGGTGATGTGCGTCTTCTCGGAGAGGGACAGAGGCCCAT M H E A L H N H Y T Q K S L S L S P G K	. = •
c	721	AAGGTGGAGGTGGTATCGAAGGTCCGACTCTGCGTCAGTGGCTGCTGCTTCTTCACCTCCACCACCACCATAGCTTCCAGGCTGAGACGCAGTCACCGACCG	
	781	BamHI AATCTCGAGGATCC	

FIG. 8

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	1			+		• • • ·	4		• • • •		-+-	· • •		+				+-,-		TGTC	60
С	61		·	- • +			4	• • • •			-+-	• • •		CAGT		CCT	CTT	ccc	CCA	C P	
С	121	CCA		CAC	CCT	CATO	SATO	TCC	CCG	GAC	ccc:	rga:	GG1	CAC	ATG	CGT	GGT	GGT(GAC	K P	180
C	181	GCC/	D ACGA	T AGA	L CCC	M rgac	I GTC	S CAAC	R STT	T	P CTG	e Sta	v cg1	T TGGA	c ccc	v CGT	V GGA	v GGT(D CAT		
c		CGG1	rgct E	TCT(D	GGG/ P	ACT(V	TTC K	F F	GTT(N	GAC(W	Y Y	GC? V	D D	GCC G	GCA V	CCT	CCAC V	GTA H	TTAC N A	
С	241	K	rctg T	TTT	P P	CGCC R	E E	CTC E	Q Q	Y	GTT(N	STC S	GTC T	CAT Y	GGC. R	ACA V	CCA V	GTC(V V	GAGT L T	300
c	301	GGC	AGGA	··+ CGT	GGT(CCTC	ACC	GAC	CTT	ACC	GTT(CT	CAT	GTT	CAC	GTT	CCA	+ · GAG(TTG	TTTC K A	
c	361	GGG/	·	+ TCG	GGG	STAC	CTC	TT	rtco	 GTA	GAG(ITT	rce	GTT	TCC	CGT	CGG	GGC	CTI	CCAC GGTG P Q	420
С	421	TCC		+ GTG	GGA		GGT	'AGC	GCC	CT	ACT(GA	CTC	+	CTT	GGT	CCA	GTC	GAC	TGGA	480
С	481	CGG2		+ GTT	rcc	SAAC	ATA	GGC	TC	 GCT(GTA	 3CG	GCA	CCT	CAC	CCT	CTC	+ · · · GTT/		CAGC GTCG Q P	
С	541		CTT	+ GTT(GAT	GTT(TGC	TGC	:GG/	 AGG	GCA(CGA	CCI	+	GCT	GCC	GAG	+	JAA G	GAGA	600
c	601	TGTC	GTT	+ CGA	GTG(CAC	CTC	TTC	CTC	GTC	CAC	CGT	CGI	ccc	CTT	GCA	GAA	GAG	CACG	AGGC S V	
С	661	ACTA	CGT	ACT	CCG	AGAC	GTC	TTC	GT	GAT	GTG(EGT	 CTI	CTC	GGA	GAG	GGA	cagi	\GGC	GGTA CCAT G K	
С	721.	TTC	CACC	TCC	ACC/	ACC#	4 \TAC	CTI	ícc <i>i</i>	AGG	-+- CTG	AGA	 CGC	AGT	CAC	 CGA	CCG	+ ACG		GCTG CGAC A G	
с	781	CACC	CACC	+ TCC	ACC	GCC	CC1	CC.	ATA	ACT	CCC	GGG	TTC	GGA	AGC	GGT	TAC	+ · CGA	ACGI	GCAC CGTG A R	
					ъ.	amU1	r														

BamH1

FIG. 9

	}	aI IU. J
	1	CTAGATTTGTTTTAACTAATTAAAGGAGGAATAACATATGATCGAAGGTCCGACTCTGC
c		GATCTAAACAAAATTGATTAATTTCCTCCTTATTGTATACTAGCTTCCAGGCTGAGACG M I E G P T L R -
	61	TCAGTGGCTGGCTGCTGCTGCGGGGGGGGGGGGGGGGGG
c	121	Q W L A A R A G G G G G G I E G P T - CCTTCGCCAATGGCTTGCAGCACGCGCAGGGGGGAGGGGGGGACAAAACTCACACAT++++++
C	121	GGAAGCGGTTACCGAACGTCGTGCGCGTCCCCCTCCGCCACCCCTGTTTTGAGTGTGTA LRQWLAARAGGGGGGGCACCCCTGTTTTGAGTGTGTA
	181	TCCACCTTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTTTTCCTCTTTCCCCCCAA++++
c		PPCPAPELLGGPSVFLFPPK-
_	241	TGGGTTCCTGTGGGAGTACTAGAGGGCCTGGGGACTCCAGTGTACGCACCACCACCTGC PKDTLMISRTPEVTCVVVVDV-
С		GAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA
c	301	CTCGGTGCTTCTGGGACTCCAGTTCAAGTTGACCATGCACCTGCCGCACCTCCACGTAT S H E D P E V K F N W Y V D G V E V H N
	361	TGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCC++++
c		A K T K P R E E Q Y N S T Y R V V S V L CACCGTCCTGCACCAGGACTGCCTGAATGGCAAGGAGTACAAGTGCCAAGGTCTCCAACA
c	421	GTGGCAGGACGTGGTCCTGACCGACTTACCGTTCCTCATGTTCACGTTCCAGAGGTTGT T V L H Q D W L N G K E Y K C K V S N K
_	481	AGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
c		TCGGGAGGTCGGGGTAGCTCTTTTGGTAGAGGTTTCGGTTTCCCGTCGGGGCTCTTG A L P A P I E K T I S K A K G Q P R E P
	541	ACAGGTGTACACCCTGCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGA+
С		Q V Y T L P P S R D E L T K N Q V S L T - CTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC
c	601	GACGGACCAGTTTCCGAAGATAGGGTCGCTGTAGCGGCACCTCACCCTCTCGTTACCCG C L V K G F Y P S D I A V E W E S N G Q
	661	GCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCC
С		CGGCCTCTTGTTGATGTTCTGGTGCGGAGGGGCACGACCTGAGGCTGCCGAGGAAGAAGG PENNYKTTPPVLDSDGSFFL-
	721	CTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCT+++++++++
С		Y S K L T V D K S R W Q Q G N V F S C S -
c	781	GCACTACGTACTCCGAGACGTGTTGGTGATGTGCGTCTTCTCGGAGAGGGACAGAGGCC V M H E A L H N H Y T Q K S L S L S P G
		BamHI
	841	TAAATAATGGATCC
C		K •

XbaI

FIG. 10

		 TCTAG					T 3 3 1	TVTI X	330	7036	-02	nma:		n a mv	ነ እ ጥረ	נגסי	ACCT	ccc	יאריז	ירייוניר	
	1			-+-			• -+	• • •			• + - •	• • • •		+ -	· • • ·	• • • •	1			+	- 60
	_	AGATC	TAA	ACA	AAA	TTG.	ATŤ	TAA	TTC	CTC	CTT	rat:	rgti								
C														M	1	E	G	P	T	L K	•
		GTCAG																			
		CAGTC																			
c ·			W	L	A	A	R .	A	G	G	G	G	G	D	K	T	H	T	C	P P	•
		CTTGC	CCA	GCA	ССТ	GAA	стс	стс	GGC	GG2	ACC	GTC	AGT"	rttc	сто	CTT	ccc	CCA	LAA.	CCCA	L
	121			-+-			+				- + -	• • •	• • •	• • • •	·		4	· · · ·	• • •	+	180
_		GAACG	GGT P	CGT A	GGA P	CTT E	GAG L	GAC L	G G	CCC' G	rgg(P	CAG' S	rca. V	AAAC F	έGΑ(L	JAAC F	3GG(P	SGGT P	K	P R	-
_																					
	181	AGGAC		-+-			+		· ·		-+-			+ -		• • •				4	240
		TCCTG	TGG	GAG	TAC	TAG	AGG	GCC	TG	GGG/	ACT	CCA	GTG'	TAC	CA	CCA	CCAC	CTC	CAC	CTCGC	}
C	, -	D	T	L .	M	1	3	K	T	P	E.	٠٧	1	C	٧	٧	٧	D	٧	S H	,
		ACGAA																			
	241	TGCTT		•																_	300
С		E												G						A P	
		AGACA	AAG	CCG	ccc	GAG	GAG	CAG	TAC	CAA	CAG	CAC	GTA	CCG	rgt	GGT(CAG	CGT	CTO	CACCO	;
	301			-+-			+				-+-			+				+	• • • •	• • • • •	- 360
_		TCTGT	TTC K	GGC	GCC	CTC	CTC	GTC	TAI V	GTT(N	GTC	GTG T	CAT(V	GGC1	ACA(V	CCA(V	GTC(S	GCA(V	∃GA(T.	TGGC T \	;
C		-						-													
		TCCTG	CAC	CAG	GAC	TGG	CTG	AAT	rgg	CAA	GGA	GTA	CAA	GTG(CAA	GGT	CTC	CAAC	CAA	AGCCG	: . สวัก
	361	AGGAC	GTG	GTC	CTG	ACC	GAC	TT?	ACC	GTT	CCT	CAT	GTT	CAC	GTT(CCA	GAG	GTT(TT.	rcgg	3
c		L	H	Q	D	W	L	N	G	K	E	Y	K	С	K	٧	S	N	K	A I	, -
		TCCCA	GCC	ccc	ATC	GAG	AAA	ACC	CAT	CTC	CAA	AGC	CAA	AGG(GCA(GCC	CCG	AGA.	ACC	ACAGO	;
	421	AGGGT		-+-			+	ጥርር	 em a (GAG	- + •	· · · ጥርር	 Стт	• • + • ጥሮሮር	 		 מפרי	הלה + י	יככי	-	480
С		P	A	P	I	E	K	T T	I	S	K	A	K	G	Q	P	R	E	P	Q 1	<i>i</i> -
		TGTAC	יאככ	CTC	יררר	ירר ז	ጥርር	ccc	JCA'	TGA	GCT	GAC	CAA	GAA	CCA	GGT	CAG	CTC	GAC	TGC	:
	481			-+-			+				-+-	• • •		+				+		+	540
_		ACATG	_											CTT(N				GGA(L			
С		-	-	_	_										-		_			_	-
	541	TGGTC	:AAA	.GGC	TTC																; ⊦ 600
	741	ACCAC	TT	CCG	AAC	ATA	GGG	TC	CT	GTA	GCG	GCA	CCT	CAC	CCT	CTC	GTT.	ACC	CGT	cecc	2
С		V	K	G	F	Y	P	S	D	I	A ·	V	E	W	E	S	N	G	Q	P I	٠ .
		AGAAC																	CCT		
	601	TCTTC	 TTC	•+• DTG	TTC	TGC	TGC	GG	AGG	GCA				+ GCT					GGA(⊦ 660 r
С		N	N	Y	K	T	T	P	P	V	L	D	S	D	G	3	F	F	L	Y	3 .
		GCAAC	ር የ	'ACC	GTO	GAC	:AAC	AG	CAG	GTG	GCA	.GCA	GGG	GAA	CGT	CTT	CTC	ATG	CTC	CGTG	A
	661			-+-			4				-+-			• • +	• • •			+			+ 720
c		CGTTC	CGAG	TGG	CAC V	CTG D	TTC K	TC(S	GTC R	CAC W	CGT	CGT	GCC	CTT	GCA V	GAA P	JAJ. S	C	GAG S	V	Y - "
C																					
	771	TGCAT	rgac	GC1	CTC	CAC	AAC	CA	CTA	CAC	GCA • + •	GAA	GAG	CCT +	CTC	CCT	GTC	TCC +··	GGG	TAAA'	r + 780
	/21	ACCTI	<u>እ</u> ርጥር	CGA	GAC	GTO	TTC	GT	GAT	GTG	CGT	CTT	'CTC	GGA	GAG	GGA	CAG	AGG	ccc	ATTT.	A
С		H	E	A	L	Н	N	H	Y	T	Q	K	S	L	S	L	3	P	G	K	.
		Bami	HI.																		
		3 3 000	ን እ ጥረ																		
	781	AATG			789																
		TTAC	TAC	iG.																	

FIG.11

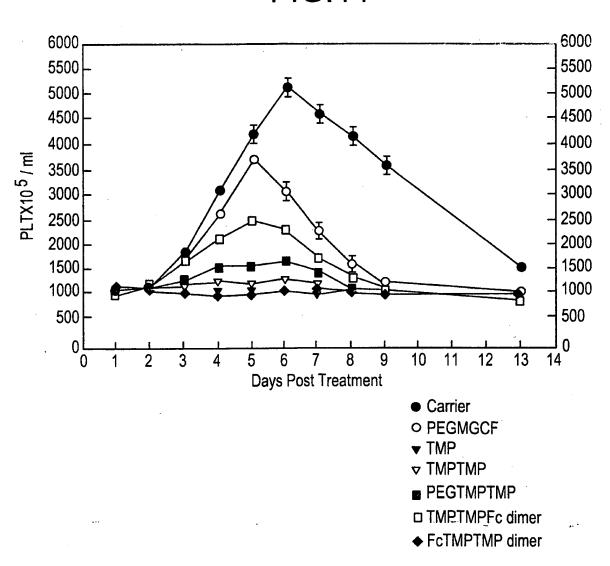
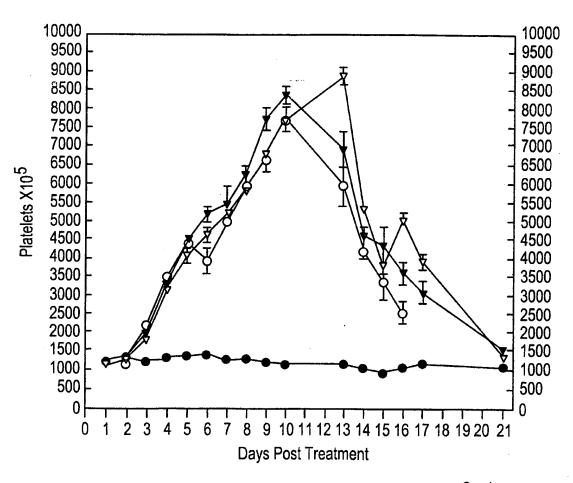


FIG.12



- Carrier
- O PEG MGDF
- ▼ TMPTMPFc dimer
- ▼ _FcTMPTMP dimer

FIG. 13

2	XbaI									ŀ		•	•	J							
1	TCTAC										ATA									C +	60
;	AGATO	TA)	LAC	AAA	ATT	GAT'	TAA	TTT	CCT	CCT	TATI	GT						_	TACA C		
61			-+				+			-+-			+				+			+	120
:	GTGGA P	C C	_																TTTT K		•
121	CCAAC	-																			180
:	GGTTC		TG	GGA	GTA	CTA	GAG	GGC	CTG	GGG.	ACTO	CAC	GTG'	PAC	GCA	CCA	CCA	CCT		T	
101	GCCAC																				240
:	CGGTC	CTI	CTC	GGG	ACTO	CCA	GTT	CAA	GTT	GAC	CATO	CAC	CTC	CCC	GCA	CCT	CCA	CGT		C	
	CCAAC	AC	\AA(GCC	GCG	GGA(GGA	GCA	GTA	CAA	CAGO	ACC	GTA	CCG'	rgt	GGT	CAG	CGT	CCTC	A	
241	GGTTC																				300
2								_											L		•
301	CCGTC		+				+			-+-			+				+	•	• • • •	+	360
2	GGCAC V	GA(GT(GGT(Q	D	GAC W	CGA L	CTT N	ACC G	GTT K	CCTC E	Y Y	GTT(K	CAC	GTT K	CCA V	GAG S	GTT N	GTTT K	'C A	
	CTCCC																				400
361	GGGAG	GG1	rcG	GGG	GTA	GCT	CTT	TTG	GTA	GAG	GTTI	CG	STT	rcc	CGT	CGG	GGC	TCT	TGGT	'G	
2	-	_		_		- •									_				P	_	•
421	AGGTO		+				+			-+-	• • - •	. - -	+	. <i>.</i> .			+	·		+	480
:	TCCAC																		CTGG T		
481	CCCT																				540
:	CGGAC	CAC V	GTT K	TCC	GAA(GAT. Y	AGG P	GTC S	GCT D	GTA I	GCGC A	CAC V	CCT(E	CAC W	CCT E	CTC S	GTT. N	ACC G	CGTC	P	•
541			+		• • •		+			• + •	• - • •		+				+			+	600
=	GCCTC				GTT(K						CGAC L								GGAG L		•
601	ACAGO		+				+		• • •	-+-			+		 -		+••			+	660
3	TGTCC S	CTT(CGA(GTG T	GCA(V	CCT	GTT K	CTC S	GTC R	CAC W	CGTO	Q Q	GCC	CTT(N	GCA V	GAA P	GAG S	TAC C	GAGC S	Y V	•
661	TGAT	GCA?	rga(GGC	TCT	GCA	CAA	CCA	CTA	CAC	GCA	GAA	GAG	CCT	CTC	CCT	GTC	TCC	GGGT	ľA.	720
001	ACTA	CGT	ACT	CCG	AGA	CGT	GTT	'GGT	GAT	GTG	CGT	TT	CTC	GGA	GAG	GGA	CAG	AGG	CCC#	T	
	AAGG?	rgg	AGG	TGG	TGG	TGG	AGG	TAC	TTA	CTC	TTG	CA	CTT	CGG	ccc	GCI	GAC	TTG	GGTT	T	700
721	TTCC	ACC'	rcc	ACC	ACC.	ACC	TCC	ATG	TAA	'GAG	AAC	3GT	GAA	GCC	GGG	ÇÇA	CTG	AAC	CCA/	VA.	
	-	-	-	-					Ban												
	GCAA	ACC	GCA	GGG	TGG	TTA	ATC	CTCC	 STGC	ATC	C										
781	CGTT		+				+			•+•	. 8	12									•

FIG. 14

	•		
		TCTAGATTTGTTTTAACTAATTAAAGGAGGAATAACATATGGGAGGTACTTACT	
c	1	AGATCTAAACAAAATTGATTAATTTCCTCCTTATTGTATACCCTCCATGAATGA	0
		ACTTCGGCCCGCTGACTTGGGTATGTAAGCCACAAGGGGGTGGGGGGAGGCGGGGGGACA	20
c	61	TGAAGCCGGGCGACTGAACCCATACATTCGGTGTTCCCCCACCCCCTCCGCCCCCCCTGT F G P L T W V C K P Q G G G G G D K -	20
	121	AAACTCACACATGTCCACCTTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTTTTCC	80
c C		TTTGAGTGTGTACAGGTGGAACGGGTCGTGGACTTGAGGACCCCCCTGGCAGTCAAAAGG T H T C P P C P A P E L L G G P S V F L -	
	181	TCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCG	40
c		AGAAGGGGGTTTTGGGTTCCTGTGGGAGTACTAGAGGGCCTGGGGACTCCAGTGTACGC FPPKFKDTLMI3RTPEVTCV	
	241	TGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCG	00
c		ACCACCACCTGCACTCGGTGCTTCTGGGACTCCAGTTCAAGTTGACCATGCACCTGCCGC V V D V S H E D P E V K F N W Y V D G V -	
	301	TGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTG	60
c	301	ACCTCCACGTATTACGGTTCTGTTTCGGCGCCCTCCTCGTCATGTTGTCGTGCATGGCAC E V H N A K T K P R E E Q Y N S T Y R V -	••
	361	TGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCA	20
С	,,,,	ACCAGTCGCAGGAGTGGCAGGACGTGGTCCTGACCGACTTACCGTTCCTCATGTTCACGT V S V L T V L H Q D W L N G K E Y K C K -	
	421	AGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGC	80
c	421	TCCAGAGGTTGTTTCGGGAGGGTCGGGGGTAGCTCTTTTGGTAGAGGTTTCGGTTTCCCG V S N K A L P A P I E K T I S K A K G Q -	00
	491	AGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACC	40
С	•••	TCGGGGCTCTTGGTGCCACATGTGGGACGGGGCGGTAGGGCCCTACTCGACTGGTTCTTGG P R E P Q V Y T L P P S R D E L T K N Q -	
	541	AGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGG	00
С		TCCAGTCGGACTGGACGACCAGTTTCCGAAGATAGGGTCGCTGTAGCGGCACCTCACCC V S L T C L V K G F Y P S D I A V E W E -	
	601	AGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACG	60
С		TCTCGTTACCCGTCGGCCTCTTGTTGATGTTCTGGTGCGGAGGGCACGACCTGAGGCTGC S N G Q P E N N Y K T T P P V L D S D G -	
	661	GCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACG	20
С	002	CGAGGAAGAAGGAGATGTCGTTCGAGTGGCACCTGTTCTCGTCCACCGTCGTCCCCTTGC S F F L Y S K L T V D K S R W Q Q G - N V	
	721	TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCT + 7	80
c		AGAAGAGTACGAGGCACTACGTACTCCGAGACGTGTTGGTGATGTGCGTCTTCTCGGAGA F S C S V M H E A L H N H Y T Q K S L S -	
		BamHI	
		CCCTGTCTCCGGGTAAATAATGGATCC	
	781	GGGACAGAGGCCCATTTATTACCTAGG	

XbaI

FIG. 15

	•	TCTAGATTTGAGTTTTAACTTTTAGAAGGAGGAATAAAATATGGGAGGTACTTACT	0
b	1	AGATCTAAACTCAAAATTGAAAATCTTCCTCCTTATTTTATACCCTCCATGAATGA	-
	61	CCACTTCGGCCCACTGACTTGGGTTTGCAAACCGCAGGGTGGCGGCGGCGGCGGCGGCGGCGG	20
ъ	01	GGTGAAGCCGGGTGACTGAACCCAAACGTTTGGCGTCCCACCGCCGCCGCCGCCGCCACC H F G P L T W V C K P Q G G G G G G G G	
	121	TACCTATTCCTGTCATTTTGGCCCGCTGACCTGGGTATGTAAGCCACAAGGGGGTGGGGG	80
b		ATGGATAAGGACAGTAAAACCGGGCGACTGGACCCATACATTCGGTGTTCCCCCACCCCC T Y S C H F G P L T W V C K P Q G G G G	
	181	AGGCGGGGGGACAAAACTCACACATGTCCACCTTGCCCAGCACCTGAACTCCTGGGGGG	240
ь		TCCGCCCCCCTGTTTTGAGTGTGTACAGGTGGAACGGGTCGTGGACTTGAGGACCCCCC G G G D K T H T C P P C P A P E L L G G	•
	241	ACCGTCAGTTTTCCTCTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCC	300
þ		TGGCAGTCAAAAGGAGAGGGGGGTTTTGGGTTCCTGTGGGAGTACTAGAGGGCCTGGGG PSVFLFPPKPKDTLMISRTP-	
	301		360
b		ACTCCAGTGTACGCACCACCACCTGCACTCGGTGCTTCTGGGACTCCAGTTCAAGTTGAC E V T C V V V D V S H E D P E V K F N W	
		GTACGTGGACGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAA	
ь	361	CATGCACCTGCCGCACCTCCACGTATTACGGTTCTGTTTCGGCGCCCCTCCTCGTCATGTT Y V D G V E V H N A K T K P R E E Q Y N	
		CAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAA	
b	421	GTCGTGCATGGCACACCAGTCGCAGGAGTGGCAGGACGTGGTCCTGACCGACTTACCGTT S T Y R V V S V L T V L H Q D W L N G K	
	481	GGAGTACAAGTGCAAGACCTCCCAACCACCCCCATCGAGAAAACCATCTC	540
b	401	CCTCATGTTCACGTTCCAGAGGTTGTTTCGGGAGGGTCGGGGGTAGCTCTTTTGGTAGAG E Y K C K V S N K A L P A P I E K T I S	•
	541	CAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGA	500
b		GTTTCGGTTTCCCGTCGGGGCTCTTGGTGTCCACATGTGGGACGGGGGTAGGGCCCTACT K A K G Q P R E P Q V Y T L P P S R D E	-
	601		660
b		CGACTGGTTCTTGGTCCAGTCGGACTGGACCAGTTTCCGAAGATAGGGTCGCTGTA L T K N Q V S L T C L V K G F Y P S D I	•
	661	CGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGT	720
b		GCGGCACCTCACCCTCTCGTTACCCGTCGGCCTCTTGTTGATGTTCTGGTGCGGAGGGCA A V E W E S N G Q P E N N Y K T T P P V	•
		GCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTG	720
ь	721	CGACCTGAGGCTGCCGAGGAAGAAGGAGATGTCGTTCGAGCACCTGTTCTCGTCCAC L D S D G S F F L Y S K L T V D K S R W	
		GCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC	040
ь	781	CGTCGTCCCCTTGCAGAAGAGTACGAGGCACTACGTACTCCGAGACGTGTTGGTGATGTG Q Q G N V F S C S V M H E A L H N H Y T	
		BamHI	
		GCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATAATGGATCC	
	841	CGTCTTCTCGGAGAGGGAGAGGCCCATTTATTACCTAGG	
b		Q K S L S L S P G K * SUBSTITUTE SHEET (RULE 26)	
		₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩	

FIG. 16 XbaI TCTAGATTTGTTTTAACTAATTAAAGGAGGAATAACATATGGACAAAACTCACACATGTC AGATCTAAACAAAATTGATTAATTTCCTCCTTATTGTATACCTGTTTTGAGTGTGTACAG M D K T H T C P -C CACCTTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTTTTCCTCTTCCCCCCAAAAC GTGGAACGGTCGTGGACTTGAGGACCCCCCTGGCAGTCAAAAGGAGAAGGGGGGTTTTG C PCPAPELLGGPSVFLFPPKP-CCAAGGACACCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGA 121 ------ 180 GGTTCCTGTGGGAGTACTAGAGGGCCTGGGGACTCCAGTGTACGCACCACCACCTGCACT C K D T L M I S R T P E V T C V V D V S. GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATG 181 -----+ 240 CGGTGCTTCTGGGACTCCAGTTCAAGTTGACCATGCACCTGCCGCACCTCCACGTATTAC HEDPEVKFNWYVDGVEVHNA-C CCAAGACAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCA GGTTCTGTTTCGGCGCCCTCCTCGTCATGTTGTCGTGCATGGCACACCAGTCGCAGGAGT c K T K P R E E Q Y N S T Y R V V S V L CCGTCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAG GGCAGGACGTGGTCCTGACCGACTTACCGTTCCTCATGTTCACGTTCCAGAGGTTGTTTC C V L H Q D W L N G K E Y K C K V S N K A -CCCTCCCAGCCCCCATCGAGAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCAC 361 ------ 420 GGGAGGGTCGGGGGTAGCTCTTTTGGTAGAGGTTTCGGTTTCCCGTCGGGGCTCTTGGTG c L P A P I E K T I S K A K G Q P R E P O -AGGTGTACACCCTGCCTCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCT TCCACATGTGGGACGGAGGTAGGGCCCTACTCGACTGGTTCTTGGTCCAGTCGGACTGGA C YTLPPSRDELTKNQVSLTC-GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGC CGGACCAGTTTCCGAAGATAGGGTCGCTGTAGCGGCACCTCACCCTCTCGTTACCCGTCG c LVKGFYPSDIAVEWESNGOP CGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCT 541 -----+ 600 GCCTCTTGTTGATGTTCTGGTGCGGAGGGCCACGACCTGAGGCTGCCGAGGAAGAAGGAA c ENNYKTTPPVLDSDGSFF ACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCG TGTCGTTCGAGTGGCACCTGTTCTCGTCCACCGTCGTCCCCTTGCAGAAGAGTACGAGGC C S K L T V D K S R W Q Q G N V F S C S TGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTA ACTACGTACTCCGAGACGTGTTGGTGATGTGCGTCTTCTCGGAGAGGGGACAGAGGCCCAT C M H E A L H N H Y T Q K S L S L S P G K -AAGGTGGAGGTGGCGGAGGTACTTACTCTTGCCACTTCGGCCCACTGACTTGGGTTT 721 -----+ 780 TTCCACCTCCACCACCGCCTCCATGAATGAGAACGGTGAAGCCGGGTGACTGAACCCAAA c G G G G G G T Y S C H F G P L T W GCAAACCGCAGGTGGCGGCGGCGGCGGCGGTGGTACCTATTCCTGTCATTTTGGCCCGC 781 -----+ 840 CGTTTGGCGTCCCACCGCCGCCGCCGCCACCATGGATAAGGACAGTAAAACCGGGCG c K P Q G G G G G G G T Y S C H P G P L -BamHI TGACCTGGGTATGTAAGCCACAAGGGGGTTAATCTCGAGGATCC ACTGGACCCATACATTCGGTGTTCCCCCAATTAGAGCTCCTAGG c TWVCKPQGG *

FIG. 17A

[AatII sticky end] (position #4358 in pAMG21)

- 5' GCGTAACGTATGCATGGTCTCC-
- 3' TGCACGCATTGCATACGTACCAGAGG-
- -CCATGCGAGAGTAGGGAACTGCCAGGCATCAAATAAAACGAAAGGCTCAGTCGAAAGACT -GGTACGCTCTCATCCCTTGACGGTCCGTAGTTTATTTTGCTTTCCGAGTCAGCTTTCTGA -
- GGGCCTTTCGTTTATCTGTTGTTGTCGGTGAACGCTCTCCTGAGTAGGACAAATCCGC CCCGGAAAGCAAAATAGACAACAAACAGCCACTTGCGAGAGGACTCATCCTGTTTAGGCG -
- -CGGGAGCGGATTTGAACGTTGCGAAGCAACGGCCCGGAGGGTGGCGGGCAGGACGCCCGC--GCCCTCGCCTAAACTTGCAACGCTTCGTTGCCGGGCCTCCCACCGCCCGTCCTGCGGGCG-
- -CATAAACTGCCAGGCATCAAATTAAGCAGAAGGCCATCCTGACGGATGGCCTTTTTGCGT--GTATTTGACGGTCCGTAGTTTAATTCGTCTTCCGGTAGGACTGCCTACCGGAAAAACGCA-

AatII

- TTCTACAAACTCTTTTGTTTATTTTTCTAAATACATTCAAATATGGACGTCGTACTTAAC AAGATGTTTGAGAAAACAAATAAAAAGATTTATGTAAGTTTATACCTGCAGCATGAATTG -
- TTTTAAAGTATGGGCAATCAATTGCTCCTGTTAAAATTGCTTTAGAAATACTTTGGCAGC AAAATTTCATACCGTTAGTTAACGAGGACAATTTTAACGAAATCTTTATGAAACCGTCG-
- -GGTTTGTTGTATTGAGTTTCATTTGCGCATTGGTTAAATGGAAAGTGACCGTGCGCTTAC -CCAAACAACATAACTCAAAGTAAACGCGTAACCAATTTACCTTTCACTGGCACGCGAATG -
- TACAGCCTAATATTTTTGAAATATCCCAAGAGCTTTTTCCTTCGCATGCCCACGCTAAAC ATGTCGGATTATAAAAACTTTATAGGGTTCTCGAAAAAGGAAGCGTACGGGTGCGATTTG -
- -GATAATTATCAACTAGAGAAGGAACAATTAATGGTATGTTCATACACGCATGTAAAAATA--CTATTAATAGTTGATCTCTTCCTTGTTAATTACCATACAAGTATGTGCGTACATTTTTAT-
- AACTATCTATATAGTTGTCTTTCTCTGAATGTGCAAAACTAAGCATTCCGAAGCCATTAT TTGATAGATATATCAACAGAAAGAGACTTACACGTTTTGATTCGTAAGGCTTCGGTAATA -
- TAGCAGTATGAATAGGGAAACTAAACCCAGTGATAAGACCTGATGATTTCGCTTCTTTAA ATCGTCATACTTATCCCTTTGATTTGGGTCACTATTCTGGACTACTAAAGCGAAGAAATT -
- -TTACATTTGGAGATTTTTTATTTACAGCATTGTTTTCAAATATATTCCAATTAATCGGTG--AATGTAAACCTCTAAAAAATAAATGTCGTAACAAAAGTTTATATAAGGTTAATTAGCCAC-
- AATGATTGGAGTTAGAATAATCTACTATAGGATCATATTTTATTAAATTAGCGTCATCAT TTACTAACCTCAATCTTATTAGATGATATCCTAGTATAAAATAATTTAATCGCAGTAGTA -
- AATATTGCCTCCATTTTTTAGGGTAATTATCCAGAATTGAAATATCAGATTTAACCATAG TTATAACGGAGGTAAAAAATCCCATTAATAGGTCTTAACTTTATAGTCTAAATTGGTATC -
- AATGAGGATAAATGATCGCGAGTAAATAATATTCACAATGTACCATTTTAGTCATATCAG-- TTACTCCTATTTACTAGCGCTCATTTATTATAAGTGTTACATGGTAAAATCAGTATAGTC-

- GCAAGTTTTGCGTGTTATATATATCATTAAAACGGTAATAGATTGACATTTGATTCTAATAA - CGTTCAAAACGCACAATATATAGTAATTTTGCCATTATCTAACTGTAAACTAAGATTATT -

FIG. 17B

- ATTGGATTTTTGTCACACTATTATATCGCTTGAAATACAATTGTTTAACATAAGTACCTG
- -TAACCTAAAAACAGTGTGATAATATAGCGAACTTTATGTTAACAAATTGTATTCATGGAC.
- -TAGGATCGTACAGGTTTACGCAAGAAAATGGTTTGTTATAGTCGATTAATCGATTTGATT-
- -ATCCTAGCATGTCCAAATGCGTTCTTTTACCAAACAATATCAGCTAATTAGCTAAACTAA-
- -CTAGATTTGTTTTAACTAATTAAAGGAGGAATAACATATGGTTAACGCGTTGGAATTCGA-
- -GATCTAAACAAAATTGATTAATTTCCTCCTTATTGTATACCAATTGCGCAACCTTAAGCT-

SacII

- -GCTCACTAGTGTCGACCTGCAGGGTACCATGGAAGCTTACTCGAGGATCCGCGGAAAGAA -
- -CGAGTGATCACAGCTGGACGTCCCATGGTACCTTCGAATGAGCTCCTAGGCGCCTTTCTT-
- GAAGAAGAAGAAGCCCGAAAGGAAGCTGAGTTGGCTGCCACCGCTGAGCAATA -
- CTTCTTCTTCTTCTGGGCTTTCCTTCGACTCAACCGACGACGGTGGCGACTCGTTAT -
- ACTAGCATAACCCCTTGGGGCCTCTAAACGGGTCTTGAGGGGTTTTTTTGCTGAAAGGAGG
- -TGATCGTATTGGGGAACCCCGGAGATTTGCCCAGAACTCCCCAAAAAACGACTTTCCTCC-
- -AACCGCTCTTCACGCTCTTCACGC 3'

[SacII sticky end]

-TTGGCGAGAAGTGCGAGAAGTG 5

(position #5904 in pAMG21)

FIG.18A - 1

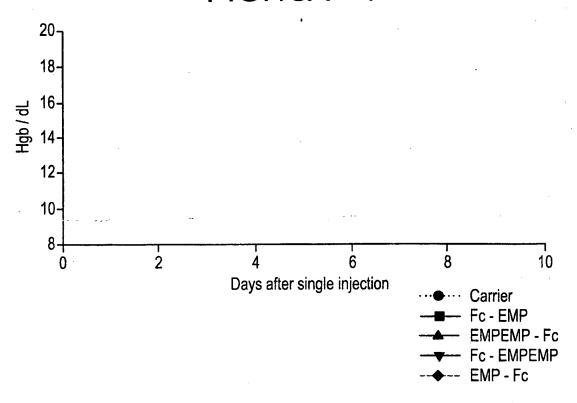


FIG.18A - 2

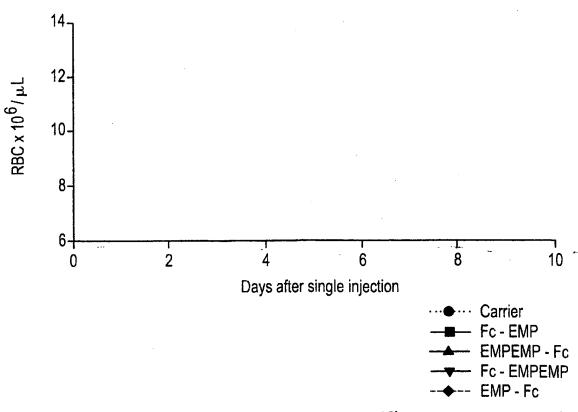


FIG.18A - 3

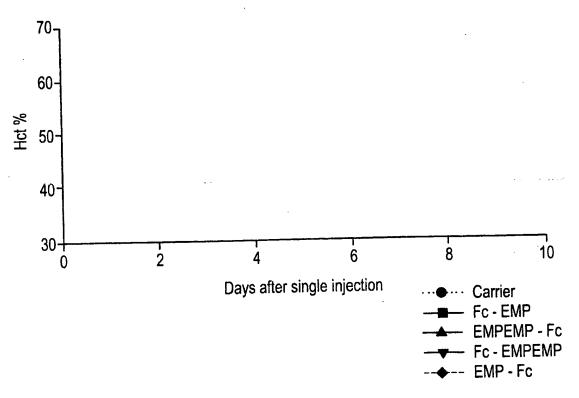


FIG.18B - 1

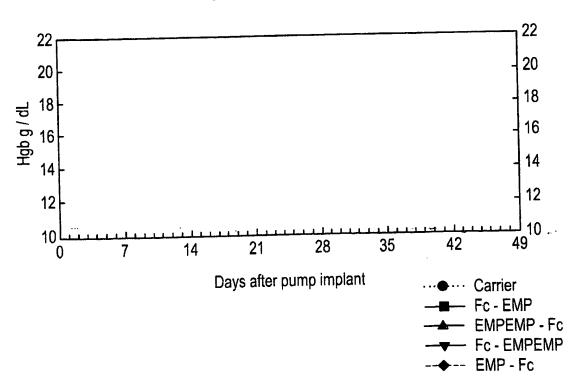


FIG.18B - 2

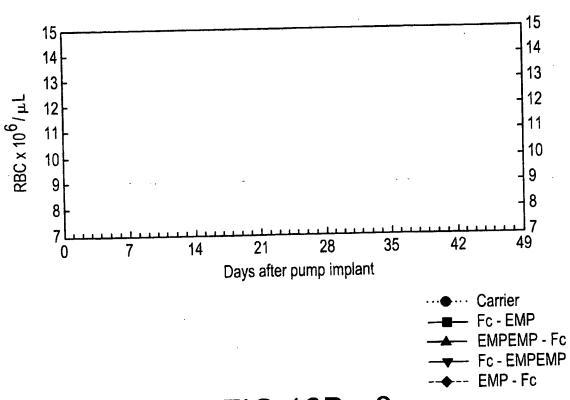


FIG.18B - 3

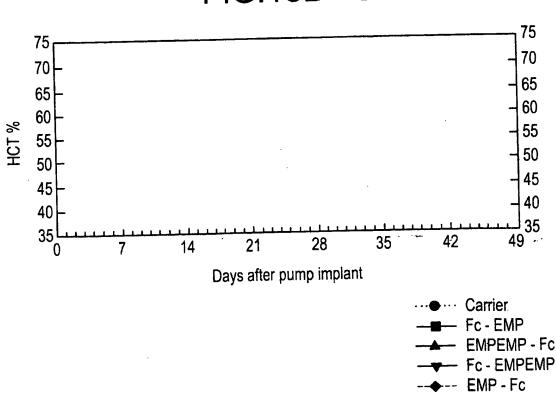


FIG. 19A NdeI CATATGGACAAAACTCACATGTCCACCTTGTCCAGCTCCGGAACTCCTGGGGGGACCG GTATACCTGTTTTGAGTGTACAGGTGGAACAGGTCGAGGCCTTGAGGACCCCCCTGGC M D K T H T C P P C P A P E L L G G P а TCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAG 61 -----+ 120 AGTCAGAAGGAGAAGGGGGGTTTTGGGTTCCTGTGGGAGTACTAGAGGGCCTGGGGACTC SVFLFPPKPKDTLMISRTPE а GTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTAC 121 ----+ 180 CAGTGTACGCACCACCTGCACTCGGTGCTTCTGGGACTCCAGTTCAAGTTGACCATG V T C V V D V S H E D P E V K F N W Y а GTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGC 181 -----+ 240 CACCTGCCGCACCTCCACGTATTACGGTTCTGTTTCGGCGCCCCTCCTCGTCATGTTGTCG V D G V E V H N A K T K P R E E Q Y N S 8 ACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAG 241 -----+ 300 TGCATGGCACACCAGTCGCAGGAGTGGCAGGACGTGGTCCTGACCGACTTACCGTTCCTC T Y R V V S V L T V L H Q D W L N G K E а TACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAA 301 -----+ 360 ATGTTCACGTTCCAGAGGTTGTTTCGGGAGGGTCGGGGGTAGCTCTTTTGGTAGAGGTTT Y K C K V S N K A L P A P I E K T I S K a GCCAAAGGGCAGCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTG 361 -----+ 420 CGGTTTCCCGTCGGGGCTCTTGGTGTCCACATGTGGGACGGGGGTAGGGCCCTACTCGAC AKGQPREPQVYTLPPSRDEL а ACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC 421 -----+ 480 TGGTTCTTGGTCCAGTCGGACTGGACGGACCAGTTTCCGAAGATAGGGTCGCTGTAGCGG T K N Q V S L T C L V K G F Y P S D I A a GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTG 481 -----+ 540 CACCTCACCCTCTCGTTACCCGTCGGCCTCTTGTTGATGTTCTGGTGCGGAGGGCACGAC V E W E S N G Q P E N N Y K T T P P V L ~ a GACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAG+ 600 CTGAGGCTGCCGAGGAAGAAGGAGATGTCGTTCGAGTGGCACCTGTTCTCGTCCACCGTC D S D G S F F L Y S K L T V D K S R W Q

FIG. 19B

601	CA	GGG	GAA	CGT	CTT	CTC	ATG	CTC	CGT	'GAT	GCA +	TGA	GGC	TCT -+-	GCA	CAA	CCA	CTA	CAC	GCAG	66
601	GT	CCC	CTT	GCA	GAA	GAG	TAC	GAG	GCA	CTA	CGT	ACT	CCG	AGA	CGT	GTT	GGT	GAT	GTG	CGTC	
	Q	G	N	V	F	S	C	s	V	M	H	E	A	L	Н	N	Н	Y	T	Q	•
661				-+-			+				+			-+-			• • +			CTAC	72
-	ТТ	CTC	GGA	GAG	GGA	CAG	AGG	CCC	CTAC	TCC	ACC	TCC	ACC	ACC	ACT	'GAA	GGA	.CGG	CGI	GATG	;
	K	S	L	s	L	S	P	G	K	G	G	G	G	G	D	F	L	P	H	Y.	•
										Ва	mH I	:									
721			ACA(-+-						. <i>-</i>	+			757	,						
	v	NT.	m	c	τ.	G	н	R	p	*											

FIG. 20A

			eI												2001		CCM	ccc	CCT	CGN	ccc	
							CCG	- + -					. .					*.				60
	•	GTA	TAC	CTC	SAAC	GAC	GGC	GTG	ATG	TTT	TTC	TGC	BAG?	\GA(CCZ	AGTG	GCA				_	
					F			••	•	K	N	T	S	L	G	н	•	•	•	<u> </u>	G	•
							CAC				4				-+-					-	•	120
	61	CC	ACC	CTC	GTT:	r T G/	AGTO	TGI	ACA	\GG7	rggi	AAC(GGG'	rcg'	TGG	ACTI	rGAG	GAC	CCC	CCT	GGC	
		G	G	D	ĸ	T	н	T	С	P	P	С	P	A	P	E	L	L	G	G	P	•
																						180
	121	AG'	rca.	AAA	GGA	GAA	GGG	GG.	rrr'	rgg	GTT	CCT	GTG	GGA	GTA	CTA	GAGO	GCC	TGC	GG#	CTC	
L		s	v	F	L	F	P	P.	ĸ	P	K	D	T	L	M	I	S	R	T	P	E	-
		GT	CAC	ATG	CGT	ggt	GGT	GGA(CGT	GAG	CCA	CGA	AGA	CCC	TGA	GGT	CAA	TT(CAAC	TG	TAC	240
	181	CA	 GTG	TAC	-+- GCA	CCA	CCA	+ CCT	GCA	CTC	GGT	GCT	TCT	GGG	ACT	CCA	GTT	CAA	GTT(GAC	CATG	
a		v	т	С	v	v	V		v	_	Н	E				v						•
•		GT.	CCA	.୯ሮር	CGT	'GGA	GGT	GCA	TAA	TGC	CAA	GAC	:AAA	\GC(cgcc	GGA	GGA	GCA	GTA	CAA	CAGC	200
	241																	•			GTCG	
				G	v	E		н		A		т	К				E	Q	Y	N	s	-
a		V	D	_	•	_	•	• •				rcci	rgci	ACC	AGG	ACTO	GCT	GAA	TGG	CAA	GGAG	
	301																				CCTC	
		_			V.		s	v	L	T			н		D		L		G		E	-
a		T	Υ	R	•	•	_	-	_	_	יררי	rcc	CAG	CCC	CCA'	TCG!	AGAA	AAC	CAT	CTC	CAA	\
	361																				GTT	
		A'	rgt'						K	_	_		_			E			I	s		•
a		Y		-			_	N			_	_		_	_		CATO	ccc	3GG/	\TG/	AGCT	3
	42																				rcga(
		C	GGT	TTC	CCG	TCG	GGG	CTC'	r r G	والآق	rcc	ACA			c	ם	g	R	D	E	L	-
a															100	mem	አጥር	CCA	cca	ACA'	L rcgc	C.
	48																				rcgc	
		T	GGT	TCT	TGG	TCC	AGT	CGG	ACT	GGA	CGG	ACC	AG I		,002			-				
a		T	K	C N	1 C) V	7 S	L	Т	C	! I	, 1	/ F	ζ. (3 I	r Y	P	5	ر.		A 	
			TGC	AGT	rGGC	AGA	GCA	ATG	GGC	AGC	CGC	AG/	\ACI	AAC'	raci	\AGA	CCA	CGC	CTC +	CCG	TGCT	·G + 600 ·C
	54		CACC	CTC	ACCC	CTCI	rcgi	TAC	CCG	TCC	الالالا	TIC.	116.	110	110							
a		ţ	<i>,</i> I	E V	N I	E 5	3 1	1 0	; Ç	} 1	? !	E 1	N I	N	Y	K 1	r 1	P) F	V	L	•

FIG. 20B

	מ	s	מ	G	s	F	F	L	Y	s	K	L	т	v	D	K	s	R	W	Q
	D	3		•	-	•	•		-	_										_
661				-+-			+				+			-+-		• • •	+			GCAG
551	GT	ccc	CTT	GCA	GAA	GAG	TAC	GAG	GCA	CTA	CGT	ACT	CCG	AGA	CGT	GTT	GGT	'GAT	GTG	CGTC
	Q	G	N	v	F	s	С	s	V	М	Н	E	A	L	н	N	н	Y	т	Q
										Ва	I Hma 	<u>.</u>	rcco							

FIG. 21A

	МQ	e r																				
	1				. 4			-+-				 -			-+			+	• • • •	• • • •	ACCG	60
		GT?	ATAC	CCTC	STTI	rtg <i>i</i>															rggc	
			М	D	ĸ	T	н	T	C	P	P	С	P	A	P	E	L	L	G	G	P	•
			AGT	CTTC	CTC	CTTC	ccc	CCA	\AA/	CCC	CAAC	GGA(CAC	CCT	CAT	GAT	CTC	CCG	GAC	ccc	rgag	120
	61	AG'	CAC	GAA(GA(GAA(GGG	GGT	rTTI	rgg(GTT(CCT	GTG	GGA	GTA	CTA	GAG	GGC	CTG	GGG	ACTC	120
		s	v	F	L	F	P	P	ĸ	P	ĸ	D	T	L	M	I	S	R	T	P	E	•
	·	GT	CAC	ATG(CGT	GT(GTC	GAC	CGTC	GAG	CCA	CGA.	AGA	CCC	TGA	GGT	CAA	GTT	CAA	CTG	GTAC	180
	121	CA	 GTG'	TAC	GCA(CCA	CCAC	CTC	CAC	CTC	GGT(GCT	TCT	GGG.	ACT	CCA	GTT	CAA	GTT	GAC	CATG	100
					v														N	W	Y	-
		GT	GGA	CGG	CGT	GGA	GGT	GCA:	raa:	rgc	CAA	GAC	AAA	GCC	GCG	GGA	GGA	GCA	GTA	CAA	CAGC	
	181											+	• • •	• • •	-+-			+			GTCG	240
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					v												_	_	_	••	_	
	241				_ 4 _			+			•	+			-+-						.GGAG	300
	241	TG	CAT	GGC	ACA	CCA	GTC	GCA	GGA	GTG	GCA	.GGA	CGT	GGI	CCT	GAC	CGA	CTI	'ACC	GTT	CCTC	
ı		T	Y	R	V	v	s	v	L	T	V	L	Н	Q	D	W	L	N	G	K	E	-
		TA	CAA	GTG	CAA	GGT	CTC	CAA	CAA	AGC	CCT	ccc	AGC	ccc	CAT	CGA	GAA	AAC	CAT	CTC	CAAA	360
	301	 TA	GTT	CAC	-+- GTT:	CCA	GAG	+ GTT	GTT	TCG	GGA	GGG	TCC	GGC	GTA	GCI	CTI	rTTC	GTA	GAG	GTTT	
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1		_			1001	ccc	ccc	አርአ	ልሮር	מימי	GGT	rGTZ	CAC	cci	rgcc	ccc	CATO	ccc	3GG2	\TG#	AGCTG	,
	361																		F		•	
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3					Q									_		_	S	R	ם		_	
	401								L			- + -							T			400
	421	T	GGT	rct	rggi	rcc?	AGTO	GG	CTC	GAC	CGG	ACC.	AGT'	TTÇ	CGA	AGA'	rag	GGT	CGC'	rgt	AGCGG	3
a		т	K	N	Q	v	S	L	T	С	L	V	K	G	F	Y	P	S	D	I	A	•
		G'	TGG	AGT(GGG	AGA	GCA,	\TG(GGC <i>I</i>	AGC	CGG	AGA	ACA	ACT.	ACA	AGA	CCA	CGC	CTC	CCG	TGCT	3 L 540
	481															• • •			T	-	ACGA(,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
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a							a a m	n c mi	mc Cr	ייריי	3 C3	GC A	AGC	TCA	CCG	TGG	ACA	AGA	GCA	GGT	GGCA	3
	543																				CCGT	
a		D	S	D	G	S	F	F	L	Y	S	K	L	, T	· V	נו	ı K	. 3	, r	. 11	I Q	

FIG. 21B

											+									+	660
601	GT	CCC	CTT	GCA	GAA	GAG	TAC	GAG	GCA	CTA	CGT	ACT	CCG	AGA	CGT	GTT	GGT	GAT	GTG	CGTC	
	Q	G	N	v	F	s	C	s	V	М	н	Ε	A	L	Н	N	Н	Y	Т	Q .	•
											. +						•			GGGT	
661	тт	CTC	GGA	GAG	GGA	CAG	AGG	CCC	CTA	TC	CACC	TCC	ACC	ACC	AAA	GCT	TAC	CTG	GGG	CCCA	
	K	S	L	s	L	s	P	G	K	G	G	G	G	G	F	E	W	T	P	G	-
	,				,					В	amH	[
721					GT?						-+-	GGAT				763	3				
	• • •																	•			

FIG. 22A

		1	- 1																		
	1	CATA	ATGT	rcga	ATG	GAC	ccc	GGG'	TTA(CTG	CAC	CCC	TAC	GC1	CTC	CCC	CTC	GG1	GGA	GGC	60
	*		racai																		
a		N	4 F	E	W	T	P	G	Y	W	Q	P	Y	A	L	P	L	G	G	G ·	•
	61		GGGZ	+ -			+		<i>-</i>	- -	+			-+	· ·	. .	- + -			+	120
a		G (3 D	ĸ	T	Н	T	c	P	P	С	P	A	P	E	L	L	G	G	P	•
		TCAC	3TTT'	TCCI	CTT	ccc	CCC.	AAA.	ACC	CAA	GGAC	CAC	CTC	CATO	CATO	CTC	ccgo	SAC	CCI	GAG	100
	121	AGTO	CAAA	AGGA	GAA	.GGG	GGG	TTT	TGG	GTT	CCT	GTG	GGA(GTAC	CTAC	JAG(3GC	TGC	3GG?	CTC	100
a		s v	v F	L	F	P	P	K	P	ĸ	D	T	L	M	I	S	R	T	P	E	•
		GTC	ACAT	GCGI	GGT	GGT	GGA	CGT	GAG	CCA	CGA	AGA	ccc	rga(GT(CAA	GTT(CAAC	CTG	STAC	240
	181	CAG	rgta	CGCA	CCA	CCA	CCT	GCA	CTC	GGT	GCT'	rcT(GGG/	ACT	CCA	GTT(CAA	3TT(GAC	CATG	240
a		v :	т с	v	v	v	D	V	S	Н	E	D	P	E	v	ĸ	F	N	W	Y	•
		GTG	GACG	GCG7	rgga	GGT	GCA	TAA	TGC	CAA	GAC	AAA	GCC	GCG	GGA(GGA(GCA	GTA	CAAC	CAGC	200
	241	CAC	CTGC	CGC	ACCT	CCA	+ CGT	ATT	ACG	GTT	+ CTGʻ	TTT(CGG	CGC	CCT	CCT	CGT	CAT	GTT(GTCG	300
a		v 1	D G	v	E	v	н	N	A	ĸ	T	K	P	R	E	E	Q	Y	N	s	-
		ACG'	TACC	GTG1	rggi	CAG	CGT	CCT	CAC	CGT	CCT	GCA	CCA	GGA	CTG	GCT	GAA'	rgg	CAA	GGAG	360
	301	TGC	ATGG	CAC	ACCA	GTC	GCA	.GGA	GTG	GCA	GGA	CGT	GGT	CCT	GAC	CGA	CTT.	ACC	GTT(CCTC	300
a ·		T .	y R	v	v	s	V	L	T	v	L	H	Q	D	W	L	N	G	K	E	-
	261		AAGT	GCA	AGGT	CTC	CAA	CAA	AGC	CCT	CCC.	AGC	ccc	CAT	CGA	GAA	AAC	CAT	CTC	CAAA	420
	361	ATG	TTCA	CGT'	rcc <i>i</i>	AGAG	GTI	'GTT	TCG	GGA	GGG	TCG	GGG	GTA	GCT	CTT	TTG	GTA	GAG	GTTT	
a		Y	K C	K	V	S	N	K	A	L	P.	A	P	I	E	K	T	I	S	K	-
	421		AAAG	GGC	AGC	ccc	AGA	ACC	ACA	GGT	GTA	CAC	CCT	GCC •+•	CCC	ATC	CCG +	GGA	TGA	GCTG +	480
	741	CGG	TTTC	CCG'	rcgo	GGC	TCT	TGG	TGT	CCA	CAT	GTG	GGA	CGG	GGG	TAG	GGC	CCT	ACT	CGAC	
a		A	K G	Q	P	R	E	P	Q	V	Y	T	L	P	P	S	R	D	E	L	•
	401	ACC	AAGA	ACC	AGG"	rcac	CCI	GAC	CTC	CCT	GGT +	CAA	AGG	CTT	CTA	TCC	CAG	CGA	CAT	CGCC	540
	401	TGG	TTCI	TGG'	TCC	AGTO	CGGA	ACTO	GAC	GGA	CCA	GTT	TCC	GAA	GAT	AGG	GTC	GCT	GTA	GCGG	<i>.</i> . •
a		T	K N	ı Q	v	S	L	T	С	L	V	K	G	F	Y	P	S	D	I	A	•
	5 11			+			4				+			-+-			+			GCTG	600
	341	CAC	CTCA	CCC	TCT	CGT?	raco	CG	rcgo	CCT	CTT	'GTT	'GAI	GTI	СТС	GTG	CGG	AGG	GCA	.CGAC	
_		37	E te	J F	S	N	G	0	P	E	N	N	Y	K	T	T	P	P	V	L	-

FIG. 22B

601				-+-			+	·			+			-+-			+		• • •	CGTC	
	D	s	D	G	s	F	F	L	Y	s	K	L	Т	v	D	K	S	R	W	Q	•
661			-	-+-			+			-ee	+	• • •		-+-			+			GCAG GCGTC	7
	Q	G	N	v	F	s	С	S	V	M	Н	E	A	L	Н	N	Н	Y	T	Q	-
										Ва	ımH I	•								•	
721				CTC -+- GAG			+				+			757	,						
		_	_	_		~	_	~	12												

FIG. 23A

	No	leI																				
	1	CAT	ATO	GGAC	CAAJ	AAC:	rca(CCC		CCT	GAZ	CTC	CTC	GGG	GGA		60
		GTA	TAC	CCT	STT?	rtg/	AGT	GTG?	rac <i>i</i>	AGGT	rggc	CAC	GGG?	rcgi	rgga	CTI	rgac	GAC	:ccc	CCT	GGC	
ı			M	D	K	Т	Н	T	С	P	P	С	P	A	P	E	L	L	G	G	P	•
	61			. <i></i> .	-+-			+		. .		 -			+		• • • •	-+-	·		GAG + CTC	120
١		s	v	F	L	F	P	P	ĸ	P	K	D	Т	L	M	I	S	R	T	P	E.	-
		GTC	AC	ATG	CGT	GGT	GGT	GGA	CGT	GAG	CAC	CGA	AGA	ccci	rgac	GTC	CAAC	TTC	CAAC	TGG	TAC	
	121	CAG	TG	rac	GCA(CCA	CCA	CCT	GCA	CTC	GGT	GCT	rct(GGG	· + - ·	CCAC	STTO	CAAC	TTC	ACC	ATG	180
ì		V	T	С	V	V	V	D	V	S	Н	E	D	P	E	V	ĸ	F	N	W	Y	•
	181	GTG	GA	CGG	CGT	GGA	GGT	GCA'	raa'	rgc	CAA	GAC	AAA	GCC	GCGC	GAG	GAG	GCAC	TAC	CAAC	AGC	240
	101	CAC	CT	GCC	GCA	CCT	CCA	CGT	ATT	ACG(GTT(CTG	TTT(CGG	CGC	CTC	CCT	CGT	CAT	TTG	TCG	210
1		v	D	G	v	E	v	Н	N	A	ĸ	T	K	P.	R	E	E	Q	Y	N	S	•
	241				-+-			+			 .	+			-+-			+ -	• • • •	• • •	GAG	300
		TGC	AT	GGC	ACA	CCA	GTC	GCA	GGA(GTG	GCA	GGA (CGT	GGT	CCT	SAC	CGA	CTT!	ACCO	TTC	CTC	
3		T	Y	R	v	V	S	V	L	T	V	L	Н	Q	D	W	L	N·	_	K	E	•
	301		AA	GTG	CAA	GGT	CTC	CAA	CAA	AGC	CCT	CCC +	AGC	CCC	CAT(CGA	GAA.	AAC(CATO	TCC	AAA	360
	301	ATG	TT	CAC	GTT	CCA	GAG	GTT(GTT'	rcg	GGA(GGG'	TCG	GGG	GTA(GCT(CTT'	rtg(GTA(SAGO	TTT	
3		Y	K	С	K	V	S	N	K	A	L	P	A	P	I	E	K	T	Ι	S	K	•
	361				-+-			+				+			-+-			+				420
		CGG	TT'	TCC	CGT	CGG	GGC	TCT'	TGG'	TGT(CCA	CAT	GTG	GGA	CGG	GGG'	rag	GGC	CTA	ACTO	CGAC	
a		A	K	G	Q	P	R	E	P	Q	•	Y	_	L	-	P	S	R	D	E	L	-
	421	ACC	AA	GAA	CCA	GGT	CAG	CCT	GAC	CTG	CCT	GGT +	CAA	AGG	CTT(- + -	CTA'	TCC	CAG(CGA	CATO	CGCC	480
	72.	TGC	STT	СТТ	GGT	CCA	GTC	GGA	CTG	GAC	GGA	CCA	GTT	TCC	GAA(GAT.	AGG	GTC	GCT(GTA(GCGG	
a		T	K	N	Q	V	S	L	T	С	L	V	K	G	F	Y	P	S	D	I	A	•
	481		GGA	GTG	GGA	GAG	CAA	TGG	GCA	GCC	GGA	GAA	CAA	CTA	CAA	GAC	CAC	GCC'	TCC	CGT	GCTG	540
	401	CAC	CCT	CAC	CCT	CTC	GTT	ACC	CGT	CGG	CCT	CTT	GTT	GAT	GTT	CTG	GTG	CGG.	AGG	GCA(CGAC	•
a		v	E	W	E	S	N	G	Q	P	E	N	N	Y	K	T	T	P	P	V	L	-
	.		CTC	CGA	CGG	CTC	CTT	CTT	CCT	CTA	CAG	CAA	GCT	CAC	CGT	GGA	CAA	GAG	CAG	GTG(GCAG	600
	541	CT	GAG	GCT	GCC	GAG	GAA	GAA	.GGA	GAT	GTC	GTT	CGA	GTG	GCA	CCT	GTT	CTC	GTC	CAC	CGTC	
a		D	s	D	G	S	F	F	L	Y	s	ĸ	L	T	v	D	K	s	R	W	Q ^r	•

FIG. 23B

	601		• • •		-+-			+				+••		• • •	-+-		• • •	+			GCAG + CGTC	
ı		Q	G	N	v	F	s	С	s	v	M	н	E	A	L	н	N	Н	Y	T	Q	-
	661	• •			-+-			+				+			-+-			+			TGAC + ACTG	720
ì		K	s	L	s	L	S	P	G	K	G	G	G	G	G	v	E	P	N	С	D .	-
														-		_	amH	Ī				
	721				-+-			+				+		AGA	-+-			+		77	3	
		т	u	17	м	W	돠	W	E	C	F	E	R	τ.	*							

FIG. 24A

	EVIC	161																				
	1		TAT(GGT'	TGA	ACC															CGT	60
		GT	ATA	CCA	ACT'	rgg	CTT	GAC	ACTO	GTA(GT1	ACAZ	ATAC	CACC	CTI	PACC	CTI	CAC	\AA/	CTI	GCA	
a			M	V	E	P	N	С	D	I	H	V	M	W	E	W	E	С	F	E	R	•
	61	• •			- + -			+			• • • •	 -			+	· -	·	-+-			CTC GAG	120
1		L	G	G	G	G	G	D	ĸ	T	н	T	С	P	P	С	P	A	P	E	L	-
		-		_																	TCC	
	121																				AGG	180
a		L	G	G	P	s	v	F	L	F	P	P	к	P	ĸ	D	T	L	M	I	s	
	181				-+-			+					• • • ·	· • • ·	+	·		-+-			AAG	240
		R		P P		v	oro. T					D							E			_
•		-	_	-	_	-	-	•	-	•		_		_		_	-	_	_		GAG	
	241				-+-			+					·		+			-+-			CTC	300
à		F	N	W	Y	V	D	G	V	E	V	Н	N	A	K	T	ĸ	P	R	E	E	•
	301																				SCTG	360
		GT	CAT	GTT(GTC	GTG	CAT	GGC/	ACA(CAC	STC	CAC	GAC	TGC	CAC	GAC	GTO	GTC	CTC	ACC	GAC	
3		_	_	N			Y					V						-	D		L	-
	361			<i>-</i>	-+-			+		· ·	·		• • •	• • • •	+		· ·	-+-	· • • •		CTTT	420
a		N	G	K	E	Y	K	С	ĸ	V.	s	N	K	A	L	P	A	P	I,	E	ĸ	
	421	• •			-+-			+				 -		. .	+		. <i></i> .	-+-	. -	. .	ATCC + TAGG	480
ā		Т	I	S	ĸ	A	ĸ	G	Q	P	R	E	P	Q	v	Y	T	L	P	P	s	•
		CG	GGA'	TGA	GCT(GAC	CAA	GAA(CCA	GT	CAG	CTC	GAC	CTG	СТС	GTC	CAA	AGG	TTC	CTAT	rccc	~40
	481																				AGGG	540
a		R	D	E	L	T	K	N	Q	v	s	L	Т	С	L	v	ĸ	G	F	Y	P	-
	541				-+-			+				 -		 ·	-+-	·		+ -	- -		CACG + GTGC	600
a		_	-																		T	-
-		_		-																		

FIG. 24B

	601	CC																			CAAG	660
	001	GG																			GTTC	
3		P	P	V	L	D	s	D	G	S	F	F	L	Y	S	K	·L	T	v	D	K	•
	661				-+-			+		• • •	• • •	+	···	- : -	-+-	• • •	• • •	+				720
		TC	GTC	CAC	CGT													CCG	AGA	CGT	GTTG	
ì		S	R	W	Q	Q	G	N	V	F	S	С	S	V	M	Н	E	A	L	H	N	•
																В	amH	I				
	721			· · ·	-+-	 .		+	·			+	• • •		ATA -+- TAT			+		77	3	
		G1.	GAI	G1 G	C G1		-1-	.002	.0710							- 0		•••	-100			
_		ᄖ	v	Ţ	٥	ĸ	S	Ť.	S	T.	S	P	G	K	*							

PCT/US99/25044

FIG. 25A

	N	ie i																				
	1	CA	PAT(GGA(CAA.	AAC'	TCA	CAC				TTG +			TCC	GGA.	ACT	CCT	GGG	GGG2	ACCG	60
		GT	ATA	CCT	GTT'	TTG.	AGT	GTG	TAC.	AGG	TGG	AAC	AGG	TCG	AGG	CCT'	rga(GGA ¹	CCC	CCC	rggc	
a			M	. D	K	T	Н	Т	С	P	P	С	P	A	P	E	L	L	G	G	P	•
	61				- + -			+	- 			+	• • •		-+-			+			rgag + actc	120
a		s	v	F	L	F	P	P	ĸ	Р	K	D	T	L	M	I	s	R	T	P	E	•
	121		• • •		-+-		• • •	+				+			- + -	· · ·		+			GTAC + CATG	180
a		v	T	С	v	v	v	D	v	s	Н	E	D	P	E	v	ĸ	F	N	W	Y	-
	181	GTO	GA(CGG	CGT	GGA	GGT	GCA				GAC				GGA	ĠGA(GCA(GTA(CAA	CAGC	240
	101	CAC	CT	GCC	GCA	CCT	CCA	CGT								CCT	CTC	CGT	CAT	TT C	STCG	240
a		v	D	G	v	E	v	Н	N	A	ĸ	T	ĸ	P	R	E	E	Q	Y	N ·	s	•
	241				-+-			+				+			-+			+			GGAG CCTC	300
a		T	Y	R	v	v	s	v	L	т	v	L	н	Q	D ·	W	L	N	G	ĸ	E	-
	301				- + -			+			•	+			-+-			+		 .	CAAA GTTT	360
a		Y	ĸ	C	K	v	s	N	ĸ		L	P	A	p	I	E	к	T	I	s	ĸ	-
	361				-+-			+				+			-+-			+			GCTG + CGAC	420
a		Α	K	G	Q	P	R	E	P	Q	V	Y	T	L	P	P	s	R	D	E	L	•
	421				-+-			+				+		-	-+-			+			CGCC + GCGG	480
a		T	K	N	Q	V	s	L	T	С	L	V	K	G	F	Y	P	S	D	I	A	-
	481				-+-			+				+			-+-	• • •.	2	+	<u></u>		GCTG + CGAC	
a		v	E	W	E	S	N	G	Q	P	E	N	N	Y	ĸ	T	T	p	P	v	L	•
	541				-+-			+				+			-+-			+		• • •	GCAG + CGTC	600
a		D	s	D	G	S	F	F	L	Y	s	ĸ	L	T	v	D	K	s	R	W	Q	•

FIG. 25B

	721			GGA	-+-			+	· •			748	3									
							mHI 															
A		ĸ	s	L	S	L	S	P	G	K	G	G	G	G	G	С	T	T	Н	W	G .	•
	661				-+-			+				+			-+-			+			CCCA	720
а		Q A A	G GAG	••	·	_	_	_				H TGG									Q GGGT	•
	601		• • •	CTT	GCA	GAA	GAG	TAC	GAG	GCA	CTA	+ CGT	ACT	CCG	-+- AGA	CGT	GTT	+ GGT	'GAT	GTG	CGTC	660

FIG. 26A

	140	1																				
	1				-+-			+	• • •		+				+		·	-+-			+	60
		GTA	TAC	CAC	GTG	GTG	GGT(GAC													CCA	
			M	С	T	T	Н	W	G	F	Т	L	С	G	G	G	G	G	D	K	G	•
	61				- + -			+			4				+	• • •		-+-	• • •	CTG GAC	+	120
																				L		_
		G GGA	G CCC	STC	G AGT:	rtte	CCT	CTT	ccc	CCC	\AA!	ACCO	CAAC	GAC	CACC	CTC	ATG	ATC	TCC	:CGG	ACC	
	121	CCI	GG	CAG	- + -	AAA	GGA	+ GAA(GGG	GGG	· · · · rtti	rggo	TTC	CTC	+	GAC	TAC	TAC	AGC	GCC	TGG	180
		G	P	s	v	F	L	F	P	P	K	P	K	D	T	L	M	I	s	R	т	-
		-																		TTC	AAC	
	181				-+-			+				+			+			• • • •	• • •		TTG	240
					т																N	
		_	_																		•	
	241				-+-			+				+			-+-	. <i>-</i>	• • • •	• • + •	• • • •		TAC	300
																					ATG	
L					D																Y	-
	301				-+-			+			 ·	+			-+-			+			'GGC	360
																3GT(CCG	
1			_		Y											Q	_			N	G	•
	361				-+-			+				+			-+-			+			ATC	420
	301	TT	CCT	CAT	GTT	CAC	GTT	CCA	GAG	GTT	GTT'	TCG	GGA	GGG'	TCG	GGG(GTA(GCT	CTT'	rtgo	TAG	
1		K	E	Y	K	С	K	v	s	N	K	A	L	P	A	P	I	E	K	T	I	٠
		TC	CAA	AGC	CAA	AGG	GCA	GCC	CCG	AGA	ACC.	ACA	GGT	GTA	CAC	CCT	GCC	CCC	ATC	CCG	GAT	480
	421	AG	 GTT	TCG	-+- GTT	TCC	CGT	CGG	GGC	TCT	TGG	TGT	CCA	САТ	GTG	GGA	CGG	GGG'	TAG	GGC(CTA	400
1		S	ĸ	Α	К	G	Q	P	R	E	P	Q	V	Y	T	L	P	P	S	R	D	-
		GA	GCT	GAC	CAA	GAA	CCA	GGI	CAG	CCT	GAC	CTG	CCT	GGT	CAA	AGG	CTT	CTA	TCC	CAG	CGAC	E 4 0
	481	CT	 CGA	CTG	-+- GTT	CTI	GGI	+ CCA	GTC	GGA	CTG	GAC	GGA	CCA	- + - GTT	TCC	GAA	GAT	AGG	GTC	GCTG	,,540
a																					D	
•		N CT	ccc	CCT	CGA	አርጥር	cca	GAG	CAA	TGG	GCA	GCC	GGA	GAA	CAA	СТА	CAA	GAC	CAC	GCC'	rccc	
	541							4				+			-+-			+			AGGG	600
_																					P	
a		1	A	V	Ŀ	77	Ŀ	3	14	3	×	•	-			-						

FIG. 26B

	601	GT	GCT	'GGA	CTC	CGA															CAGG	
	001	CA	CGA	CCT	GAG	GCI															GTCC	000
·		v	·L	D	s	D	G	s	F	F	L	Y	s	K	L	T	v	D	ĸ	S	R	-
	661				-+-			+	-,		•	+			-+-			+			CTAC	720
		W	Q									V				A		.CGT H			GATG Y	
													Ва	mHI								
	721	•••		GAA CTT	-+-			+				+			-+-		763					
		m	_	17		T	_			ъ	_	v										

SEQUENCE LISTING

<110> LIU, CHUAN-FA
 FEIGE, ULRICH
 CHEETHAM, JANET
 BOONE, THOMAS CHARLES

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<130> A-527

<140> NOT YET RECEIVED

<141> 1999-10-22

<150> 60/105,371

<151> 1998-10-23

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Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

1 5 10 15

ggg gga ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc 96
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
20 25 30

atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gtg gtg agc 144

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

35 40 45

cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

50 ... 55 60

gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac agc acg 240

Val 65	His	Asn	Ala	Lys	70	Lys	Pro	Arg	GIU	75	Gln	Tyr	Asn	ser	80	
					gtc Val											288
					tgc Cys											336
			Thr		tcc Ser		-									384
					cca Pro											432
					gtc Val 150											480
					Gly											528
					gac Asp											576
					tgg Trp											624
					cac His											672
		ggt Gly														684
<21:	2> P	28 RT UMAN		÷										na Pingan		

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Met 1	Asp	Lys	Thr	His 5	Thr	Сув	Pro	Pro	Cys 10	Pro	Ala	Pro	Glu	Leu 15	Leu
Gly	Gly	Pro	Ser 20	Val	Phe	Leu	Phe	Pro 25	Pro	Lys	Pro	Lys	Asp 30	Thr	Leu
Met	Ile	Ser 35	Arg	Thr	Pro	G1u	Val 40	Thr	Сув	Val	Val	Val 45	Asp	Val	Ser
His	Glu 50	Asp	Pro	Glu	Val	Lys 55	Phe	Asn	Trp	Tyr	Val 60	Asp	Gly	Val	Glu
Val ⁻ 65	His	Asn	Ala	Lys	Thr 70	Lys	Pro	Arg	Glu	G1u 75	Gln	туг	Asn	Ser	Thr 80
Tyr	Arg	Val	Val	Ser 85	Val	Leu	Thr	Val	Leu 90	His	Gln	Asp	Trp	Leu 95	Asn
Gly	Lys	Glu	Tyr 100	Lys	Cys	Lys	Val	Ser 105	Asn	Lys	Ala	Leu	Pro 110	Ala	Pro
Ile	Glu	Lys 115	Thr	Ile	Ser	Lys	Ala 120	Lys	Gly	Gln	Pro	Arg 125	Glu	Pro	Gln
Val	Туг 130		Leu	Pro	Pro	Ser 135	Arg	Asp	Glu	Leu	Thr 140	Lys	Asn	Gln	Val
Ser 145	Leu	Thr	Cys	Leu	Val 150	Lys	Gly	Phe	Tyr	Pro 155	Ser	Asp	Ile	Ala	Val 160
Glu	Trp	Glu	Ser	Asn 165	Gly	Gln	Pro	Glu	Asn 170		Tyr	Lys	Thr	Thr 175	Pro
Pro	Val	Leu	Asp 180	Ser	Asp.	Gly	Ser	Phe 185	Phe	Leu	Tyr	Ser	Lys 190	Leu	Thr
Val	Asp	Lys 195	Ser	Arg	Trp	Gln	Gln 200	Gly	Asn	Val	Phe	Ser 205	Cys	Ser	Val
Met	His 210	Glu	Ala	Leu	His	Asn 215	His	Tyr	Thr	Gln	Lys 220	Ser	Leu	Ser	Leu
Ser	Pro	Gly	Lys												

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<210> 3
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Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala
                                     10
Arg Ala
<210> 4
<211> 18
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: PEGYLATED
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                                     10
Arg Ala
<210> 5
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<212> DNA
<213> Artificial Sequence
<223> Description of Artificial Sequence:Fc-TMP
<220>
<221> CDS
<222> (39)..(779)
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<400> 5 tctagatttg ttttaactaa ttaaaggagg aataacat atg gac aaa act cac aca 56 Met Asp Lys Thr His Thr 1 tgt cca cct tgt cca gct ccg gaa ctc ctg ggg gga ccg tca gtc ttc Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe 10 15 152 ctc ttc ccc cca aaa ccc aag gac acc ctc atg atc tcc cgg acc cct Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro 30 25 gag gtc aca tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc 200 Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val 45 aag ttc aac tgg tac gtg gac ggc gtg gag gtg cat aat gcc aag aca 248 Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr 65 `55 60 aag ccg cgg gag gag cag tac aac agc acg tac cgt gtg gtc agc gtc 296 Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val 80 75 ctc acc gtc ctg cac cag gac tgg ctg aat ggc aag gag tac aag tgc 344 Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys 90 95 392 aag gtc tcc aac aaa gcc ctc cca gcc ccc atc gag aaa acc atc tcc Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser 105 aaa gcc aaa ggg cag ccc cga gaa cca cag gtg tac acc ctg ccc cca Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro 120 125 tcc cgg gat gag ctg acc aag aac cag gtc agc ctg acc tgc ctg gtc Ser Arg Asp Glu. Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val 145 140 135 aaa ggc ttc tat ccc agc gac atc gcc gtg gag tgg gag agc aat ggg

cag ccg gag aac aac tac aag acc acg cct ccc gtg ctg gac tcc gac 584
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

160

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly

155

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180 175 170

ggc tcc ttc ttc ctc tac agc aag ctc acc gtg gac aag agc agg tgg Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp 195 185 190

cag cag ggg aac gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His 205 200

aac cac tac acg cag aag age etc tee etg tet eeg ggt aaa ggt gga 728 Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly 225 215 220

ggt ggt ggt atc gaa ggt ccg act ctg cgt cag tgg ctg gct gct cgt Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg 240 235

794 gct taatctcgag gatcc Ala

<210> 6

<211> 247

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence:Fc-TMP

<400> 6

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu 10

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu 30 25 20

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser 40 45 35

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu 60 50 55

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr 70 65

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn 90 85

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val 130 135 140

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val 145 150 155 160

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro 165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr 180 185 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val 195 200 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu 210 215 220

Ser Pro Gly Lys Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg
225 230 235 240

Gln Trp Leu Ala Ala Arg Ala 245

<210> 7

<211> 861

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Fc-TMP-TMP

<220>

<221> CDS

<222> (39)..(842)

<400> 7

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Met Asp Lys Thr His Thr
1 5

tgt	cca	cct	tgt	cca	gct	ccg	gaa	ctc	ctg	ggg	gga	ccg	tca	gtc	ttc	104
Суз	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Glv	Glv	Pro	Ser	Val	Phe	
•			10					15			1		20			
			10					10					20			
ctc	ttc	CCC	cca	aaa	ccc	aag	gac	acc	ctc	atg	atc	tcc	cgg	acc	cct	152
Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	
		25					30					35			•	
																200
	-		-		gtg		•	• •	•		•	-			· .	200
Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	
	40					45					50					
aag	ttc	aac	taa	tac	gtg	σac	aac	ata	gag	ata	cat	aat	acc	aaq	aca	248
_					Val	-								-		
_	FIIC	VOII	ΙΙĐ	TAT		veħ	GIY	Val	GIU		ura	VOII	Vid	шyз		
55					60					65					70	
aag	ccg	cgg	gag	gag	cag	tac	aac	agc	acg	tac	cgt	gtg	gtc	agc	gtc	296
Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	-
-	* *			75		-			80	_				85		
				. •					•							
																244
					cag											344
Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	
			90					95					100			
аад	atc	tcc	aac	aaa	gcc	ctc	cca	acc	ccc	atc	σασ	aaa	acc	atc	tcc	392
-	-				Ala											
пÃа	vai		ASII	пЛя	MIG	nea		MIG	FIO	116	Gru		1111	116	261	
•		105					110					115				
		•														
aaa	gcc	aaa	ggg	cag	ccc	cga	gaa	cca	cag	gtg	tac	acc	ctg	CCC	cca	440
Lys	Ala	Lys	Gly	Gln	Pro.	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	
-	120	-	•			125					130					
																400
					acc											488
Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Суѕ	Leu		
135					140					145					150	
					٠.											
aaa	aac	ttc	tat	ccc	agc	gac	atc	qcc	gta	gag	tạq	gag	agc	aat	ggg	536
					Ser											
пув	GIĀ	Pne	туг		Ser	Asp	TIE	ATG		Giu	TTD	GIU	DCI		011	
				155					160					165		
cag	ccg	gag	aac	aac	tac	aag	acc	acg	cct	CCC	gtg	ctg	gac	tcc	gac	584
					Tyr											
			170		-	-	-	175					180			
			-,0					•								
								_, -					2		+ a a	632
					tac											034
Gly	Ser	Phe	.Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Lrp	
		185					190					195			-	

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728

861

cag cag ggg aac gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His 205 200 210 aac cac tac acg cag aag agc ctc tcc ctg tct ccg ggt aaa ggt gga Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly 220 225 215 ggt ggt ggt atc gaa ggt ccg act ctg cgt cag tgg ctg gct gct cgt Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg 235 240 245 get ggt ggt ggc ggc ggc gga ggt att gag ggc cca acc ett ege 824 Ala Gly Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg 255 caa tgg ctt gca gca cgc gcataatctc gaggatccg Gln Trp Leu Ala Ala Arg 265 <210> 8 <211> 268 <212> PRT <213> Artificial Sequence <223> Description of Artificial Sequence:Fc-TMP-TMP <400> 8 Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu 25 Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser 40 45 35 His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu 60 55 50 Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr 75 65 70 Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn 90 85 Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro-110 105 100

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115
120
125

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asp Gln Val

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val 130 135 140

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val 145 150 155 160

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro 165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
180 185 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val 195 200 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu 210 215 220

Ser Pro Gly Lys Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg 225 230 235 240

Gln Trp Leu Ala Ala Arg Ala Gly Gly Gly Gly Gly Gly Gly Ile 245 250 255

Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg 260 265

<210> 9

<211> 855

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TMP-TMP-Fc

<220>

<221> CDS

<222> (39)..(845)

<400> 9

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-				ctg Leu												104
				cca Pro												152
				gac Asp												200
	Leu			gga Gly												248
				atc Ile 75												296
				gaa Glu												344
				cat His												392
				cgt Arg												440
tgg Trp 135	ctg Leu	aat Asn	ggc Gly	aag Lys	gag Glu 140	tac Tyr	aag Lys	tgc Cys	aag Lys	gtc Val 145	tcc Ser	aac Asn	aaa Lys	gcc Ala	ctc Leu 150	488
cca Pro	gcc Ala	ccc Pro	atc Ile	gag Glu 155	aaa Lys	acc Thr	atc Ile	tcc	aaa Lys 160	Ala	aaa Lys	ggg	cag Gln	ccc Pro 165	cga Arg	536
gaa Glu	cca Pro	cag Gln	gtg Val 170	Tyr	acc Thr	ctg Leu	ccc	cca Pro 175	tcc Ser	cgg	gat Asp	gag Glu	ctg Leu 180	Thr	aag	584

aac cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp

632

185 190 195

atc gcc gtg gag tgg gag agc aat ggg cag ccg gag aac aac tac aag 680

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys

200 205 210

acc acg cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc 728

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser

215 220 225 230

aag ctc acc gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca 776
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
235 240 245

tgc tcc gtg atg cat gag gct ctg cac aac cac tac acg cag aag agc

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser

250 255 260

ctc tcc ctg tct ccg ggt aaa taatggatcc 855
Leu Ser Leu Ser Pro Gly Lys
265

<210> 10

<211> 269

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence: TMP-TMP-Fc

<400> 10

Met Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly
1 5 10 15

Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp 20 25 30

Leu Ala Arg Ala Gly Gly Gly Gly Gly Asp Lys Thr His Thr Cys
35 40 45

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu 50 55 60

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu 65 70 75 80

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys 85 90 95

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
100 105 110

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu 115 120 125

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
130 135 140

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys 145 150 155 160

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser 165 170 175

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys 180 185 190

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
195 200 205

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly 210 215 220

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln 225 230 235 240

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn 245 250 255

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys 260 265

<210> 11

<211> 789

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TMP-Fc

<220>

<221> CDS

<222> (39)..(779)

<400> 11

tctagatttg ttttaactaa ttaaaggagg aataacat atg atc gaa ggt ccg act 56 Met Ile Glu Gly Pro Thr ctg cgt cag tgg ctg gct gct cgt gct ggt gga ggc ggt ggg gac aaa 104 Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly Gly Gly Asp Lys 10 15 act cac aca tgt cca cct tgc cca gca cct gaa ctc ctg ggg gga ccg 152 Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro 25 tca gtt ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg atc tcc 200 Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser 50 40 45 cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac gaa gac Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp 65 70 55 60 cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg cat aat 296 Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn 75 gcc aag aca aag ccg cgg gag gag cag tac aac agc acg tac cgt gtg Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val 90 95 100 gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc aag gag 392 Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu 105 110 tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc gag aaa Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys 130 120 125 acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca cag gtg tac acc 488 Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr 135 140 150 ctg ccc cca tcc cgg gat gag ctg acc aag aac cag gtc agc ctg acc 536 Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr 160 155 tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag tgg gag 584 Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 180 175 170

age aat ggg cag ccg gag aac aac tac aag acc acg cct ccc gtg ctg 632 Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 185 gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg gac aag 680 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 205 210 age agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg atg cat gag Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu 215 220 225 230 get etg cac aac cac tac acg cag aag age etc tee etg tet eeg ggt 776 Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly 240 245 235 aaa taatggatcc 789 Lys <210> 12 <211> 247 <212> PRT <213> Artificial Sequence <223> Description of Artificial Sequence: TMP-Fc Met Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly 15 1 5 10 Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro 20 25 30 Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys 35 40 Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val 60 55 Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp 75 70 Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr 90 85 Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp 100 105

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu 115 120 125

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg 130 135 140

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
145 150 155 160

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp 165 170 175

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
180 185 190

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser 195 200 205

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser 210 225 220

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser 225 230 235 240

Leu Ser Leu Ser Pro Gly Lys 245

<210> 13

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TMP

<400> 13

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
1 5 10

<210> 14

<211> 36

<212> PRT

<213> Artificial Sequence

<220> <223> Description of Artificial Sequence: TMP-TMP <400> 14 Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly 10 Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu 25 Ala Ala Arg Ala 35 <210> 15 <211> 812 <212> DNA <213> Artificial Sequence <223> Description of Artificial Sequence:Fc-EMP <220> <221> CDS <222> (39)..(797) <400> 15 tctagatttg ttttaactaa ttaaaggagg aataacat atg gac aaa act cac aca 56 Met Asp Lys Thr His Thr tgt cca cct tgt cca gct ccg gaa ctc ctg ggg gga ccg tca gtc ttc 104 Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe 20 15 10 ctc ttc ccc cca aaa ccc aag gac acc ctc atg atc tcc cgg acc cct 152 Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro 30 25 gag gtc aca tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc 200 Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val 50 45 40 aag ttc aac tgg tac gtg gac ggc gtg gag gtg cat aat gcc aag aca Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

60

65

aag Lys	ccg Pro	cgg Arg	gag Glu	gag Glu	cag Gln	tac Tyr	aac Asn	agc Ser	acg Thr	tac Tyr	cgt Arg	gtg Val	gtc Val	Ser	gtc Val	296
				75					80					83		344
ctc Leu	acc Thr	gtc Val	ctg Leu 90	cac His	Gln	gac Asp	tgg Trp	Leu 95	Asn	Gly	Lys	Glu	Tyr 100	Lys	Сув	
aag Lys	gtc Val	tcc Ser	Asn	aaa Lys	gcc Ala	ctc Leu	cca Pro 110	gcc Ala	ccc Pro	atc Ile	gag Glu	aaa Lys 115	acc Thr	atc Ile	tcc Ser	392
aaa Lys	gcc Ala 120	aaa Lys		cag Gln	ccc Pro	cga Arg 125	gaa Glu	cca Pro	cag Gln	gtg Val	tac Tyr 130	acc Thr	ctg Leu	ccc	cca Pro	440
tcc Ser	cgg	~a+	gag Glu	ctg Leu	acc Thr	Lys	aac Asn	cag Gln	gtc	agc Ser 145	rea	acc	tgc Cys	ctg Leu	gtc Val 150	488
aaa Lys	ggc Gly	tto Phe	e tat	ccc Pro	Ser	gac Asp	ato Ile	gcc Ala	gtg Val 160	GIU	tgg Trp	gag Glu	ago Ser	aat Asr 165	ggg Gly	536
caç Glr	g ccq	ga Gl	g aa u Asi 17	n Ası	tac Tyr	aaq Lys	acc Thr	acg Thr	Pro	ccc Pro	gtg Val	ctg Lev	gad Asi 180		gac Asp	584
gg: Gl:	c tc y Se	c tt r Ph 18	e Ph	c cto	tac	c ago	2 aaq 2 Ly:	s Lei	acc Thr	gtç Va	l ysi	c aaq p Lys 199	. JE	c ago	g tgg g Trp	632
ca G1	g ca n G1 20	g gg n Gl		c gt n Va	c tte 1 Ph	c tc e Se 20	r Cy	c tco s Se:	c gtq r Val	g ato	g car t Hi: 21	8 91	g gc u Al	t ct a Le	g cac u His	680
aa As 21	c ca n Hi		ac ac	eg ca nr Gl	g aa n Ly 22	s Se	c ct r Le	c tc u Se	c cte	g to u Se 22	I PL	g gg o Gl	t aa y Ly	a gg s Gl	t gga y Gly 230	728
		gt go Ly G	gt go	ga gg ly Gl 21	y Th	t ta	c to	et tg er Cy	c ca s Hi 24	S PI	c gg ne Gl	y Pr	g ct		et tgg nr Trp 15	776
gt Vá	tt to	gc a ys L	ys P	cg ca ro G	ag ge	gt gq Ly G:	gt ta Ly	aatct	cgtq:	g gat	cc			e Sapan	-	812

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<210> 16

<211> 253

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence: Fc-EMP

<400> 16

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu 10 5

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu 25 20

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Asp Val Ser 40

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu 55

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr 75 70

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro 105 100

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln 120 115

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val 135 130

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val 155 150 145

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro 175 170 165

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr 190 180

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val 205 200 195

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu

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220 215 210

Ser Pro Gly Lys Gly Gly Gly Gly Gly Gly Thr Tyr Ser Cys His 235 230

Phe Gly Pro Leu Thr Trp Val Cys Lys Pro Gln Gly Gly 250 245

<210> 17

<211> 807

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EMP-Fc

<220>

<221> CDS

<222> (39)..(797)

<400> 17

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tgc cac ttc ggc ccg ctg act tgg gta tgt aag cca caa ggg ggt ggg Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys Pro Gln Gly Gly 15 10

gga ggc ggg ggg gac aaa act cac aca tgt cca cct tgc cca gca cct 152 Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro 30 25

gaa ctc ctg ggg gga ccg tca gtt ttc ctc ttc ccc cca aaa ccc aag 200 Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys 50 45 40

gac acc ctc atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val 60

gac gtg agc cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp 80 75

ggc gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac

Gly	Val	Glu	Val 90	His	Asn	Ala	Lys	Thr 95	Lys	Pro	Arg	GIU	100	GIII	Tyr	
aac Asn	agc Ser	acg Thr 105	tac Tyr	cgt Arg	gtg Val	gtc Val	agc Ser 110	gtc Val	ctc Leu	acc Thr	gtc Val	ctg Leu 115	cac His	cag Gln	gac Asp	392
tgg Trp	ctg Leu 120	aat Asn	ggc Gly	aag Lys	gag Glu	tac Tyr 125	aag Lys	tgc Cys	aag Lys	gtc Val	tcc Ser 130	aac Asn	aaa Lys	gcc Ala	ctc Leu	440
cca Pro 135	gcc Ala	ccc Pro	atc Ile	gag Glu	aaa Lys 140	acc Thr	atc Ile	tcc Ser	aaa Lys	gcc Ala 145	aaa Lys	ggg Gly	cag Gln	ccc Pro	cga Arg 150	488
gaa Glu	cca Pro	cag Gln	gtg Val	tac Tyr 155	acc Thr	ctg Leu	ccc Pro	cca Pro	tcc Ser 160	cgg Arg	gat Asp	gag Glu	ctg Leu	acc Thr 165	aag Lys	536
aac Asn	cag Gln	gtc Val	agc Ser 170	ctg Leu	acc Thr	tgc Cys	ctg Leu	gtc Val 175	aaa Lys	ggc Gly	ttc Phe	tat Tyr	ccc Pro 180	Ser	gac Asp	584
atc Ile	gcc Ala	gtg Val	Glu	tgg Trp	gag Glu	agc Ser	aat Asn 190	Gly	cag Gln	ccg Pro	gag Glu	aac Asn 195	Asn	tac Tyr	aag	632
acc Thr	acg Thr	Pro	ccc Pro	gtg Val	ctg Leu	gac Asp 205	Ser	gac	ggc Gly	tcc Ser	ttc Phe 210	Phe	cto Leu	tac Tyr	agc Ser	680
aag Lys 215	Lev	acc Thr	gtç Val	gac L Asp	aag Lys 220	Ser	agg Arg	tgg Trp	cag Gln	cag Glm 225	Gly	aac Asn	gto Val	tto Phe	tca Ser 230	728
tgo Cys	tco Sei	c gtq	g atq L Mei	cat His 235	Gli	g gct 1 Ala	ctg Lev	cac His	aac Asn 240	His	tac Tyr	acç Thi	caç Gli	g aaq n Lys 245	g agc s Ser	776
				t ccq r Pro				atgga	itcc							807

<210> 18 <211> 253 ---<212> PRT <213> Artificial Sequence <223> Description of Artificial Sequence: EMP-Fc

<4	\sim	^-	. 1	С
< 4	u	v	, т	c

- Met Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys

 1 5 10 15
- Lys Pro Gln Gly Gly Gly Gly Gly Gly Gly Asp Lys Thr His Thr Cys
 20 25 30
- Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu 35 40 45
- Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu 50 55 60
- Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
 65 70 75 80
- Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys 85 90 95
- Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu 100 105 110
- Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys 115 120 125
- Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys 130 135 140
- Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser 145 150 155 160
- Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
- Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln 180 185 190
- Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
 195 200 205
- Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln 210 215 220
- Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn 225 230 230

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys 245

19															
881															
DNA	4														
Art	ific	cial	Sequ	ence	!										
•															
											_				
Des	crip	tion	of	Arti	fici	al S	Seque	ence	EMP-	- EMP	FC				
	•														
•															
	S														
		(871))												
> 19															
ratt	tg a	gttt	taact	: tt1	taga	agga	gga	ataa	aat	atg (gga (ggt	act	tac	55
,	- •	•								Met	Gly	Gly	Thr	-1-	
										1				5	
															4.00
tac	cac	ttc	aac (cca	ctg	act	tgg	gtt	tgc	aaa	ccg	cag	ggt	ggc	103
Cvs	His	Phe	Glv :	Pro	Leu	Thr	Trp	Val	Cys	Lys	Pro	Gln	Gly	Gly	
C, D		••••						15					20		
										•					
aac	aac	aac	aat ·	aat	acc	tat	tcc	tgt	cat	ttt	ggc	ccg	ctg	acc	151
99C	G1 v	Glv	Glv	Glv	Thr	Tyr	Ser	Суз	His	Phe	Gly	Pro	Leu	Thr	
GIY	GIY		4 -3	2		-	30					35			
	+~+	220	cca	caa	aaa	aat	ggg	gga	ggc	ggg	ggg	gac	aaa	act	199
yca Val	Cre	T.V.C	Pro	Gln	Glv	Gly	Gly	Gly	Gly	Gly	Gly	Asp	Lys	Thr	
Vai		5 ,5				45	_				50				
		663	cct	tac	cca	σca	cct	gaa	ctc	ctg	ggg	gga	ccg	tca	247
aca	Cyc	Dro	Dro	Cva	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	
		PIO	FIO	CJU	60					65					
22					•										
				002	222	ccc	ааσ	gac	acc	ctc	atg	ato	tco	cgg	295
ttc	ctc	25.0	200	DEA	Lara	Dro	Lvs	Asp	Thr	Leu	Met	Ile	Ser	Arg	
	Leu	Pne	PIO	75	Lys	110			80)				85	
				/5											
				L		ato	, ata	dac	ato	ago	cac	gaa	gad	cct	343
cct	gag	gtc	aca	tgc	919	77a1	val	AST	Val	Ser	His	Gli	ı Ası	Pro	
Pro		val	rnr	Cys	val	491	. 401	95	; 				100)	
			90						-			••	•	~	
							, ,,,,,	י ממי	ate	r dad	gto	ca	t aa	t gcc	391
gto	aaq	ttc	aac	tgg	tac	, gc	y yak	, 99'	/ Vai	l Gli	val	Hi	s As	n Ala	
val	L Ly:	3 Ph€	a Asn	Trp	туг	va.	r wai	, 31)	, , ,		_ ,				
	881 DNP Art Des CD: (4' 19 gatt tgc Cys Gly gta Val aca Thr 55 ttc Phe	881 DNA Artific Descrip CDS (41) 19 gatttg a tgc cac Cys His ggc ggc Gly Gly gta tgt Val Cys 40 aca tgt Thr Cys 55 ttc ctc Phe Leu cct gag Pro Glu	881 DNA Artificial Description CDS (41)(871) 19 gatttg agttt tgc cac ttc Cys His Phe ggc ggc ggc Gly Gly Gly 25 gta tgt aag Val Cys Lys 40 aca tgt cca Thr Cys Pro 55 ttc ctc ttc Phe Leu Phe cct gag gtc Pro Glu Val	B81 DNA Artificial Seque Description of CDS (41)(871) 19 gatttg agttttaact tgc cac ttc ggc Cys His Phe Gly 10 ggc ggc ggc ggt Gly Gly Gly Gly 25 gta tgt aag cca Val Cys Lys Pro 40 aca tgt cca cct Thr Cys Pro Pro 55 ttc ctc ttc ccc Phe Leu Phe Pro cct gag gtc aca Pro Glu Val Thr 90	B81 DNA Artificial Sequence Description of Arti CDS (41)(871) 19 gatttg agttttaact ttt tgc cac ttc ggc cca Cys His Phe Gly Pro 10 ggc ggc ggc ggt ggt Gly Gly Gly Gly 25 gta tgt aag cca caa Val Cys Lys Pro Gln 40 aca tgt cca cct tgc Thr Cys Pro Pro Cys 55 ttc ctc ttc ccc cca Phe Leu Phe Pro Pro 75 cct gag gtc aca tgc Pro Glu Val Thr Cys 90	DNA Artificial Sequence Description of Artificial CDS (41)(871) 19 gatttg agttttaact tttagas tgc cac ttc ggc cca ctg Cys His Phe Gly Pro Leu 10 ggc ggc ggc ggt ggt acc Gly Gly Gly Gly Gly Thr 25 gta tgt aag cca caa ggg Val Cys Lys Pro Gln Gly 40 aca tgt cca cct tgc cca Thr Cys Pro Pro Cys Pro 55 60 ttc ctc ttc ccc cca aaa Phe Leu Phe Pro Pro Lys 75 cct gag gtc aca tgc gtg Pro Glu Val Thr Cys Val 90	DNA Artificial Sequence Description of Artificial Sequence CDS (41)(871) 19 Gatttg agttttaact tttagaagga tgc cac ttc ggc cca ctg act Cys His Phe Gly Pro Leu Thr 10 ggc ggc ggc ggt ggt acc tat Gly Gly Gly Gly Gly Thr Tyr 25 gta tgt aag cca caa ggg ggt Val Cys Lys Pro Gln Gly Gly 40 45 aca tgt cca cct tgc cca gca Thr Cys Pro Pro Cys Pro Ala 55 60 ttc ctc ttc ccc cca aaa ccc Phe Leu Phe Pro Pro Lys Pro 75 cct gag gtc aca tgc gtg gtg Pro Glu Val Thr Cys Val Val 90	B81 DNA Artificial Sequence Description of Artificial Sequence CDS (41)(871) 19 gatttg agttttaact tttagaagga gga tgc cac ttc ggc cca ctg act tgg Cys His Phe Gly Pro Leu Thr Trp 10 ggc ggc ggc ggt ggt acc tat tcc Gly Gly Gly Gly Gly Thr Tyr Ser 25 30 gta tgt aag cca caa ggg ggt ggg Val Cys Lys Pro Gln Gly Gly Gly 40 aca tgt cca cct tgc cca gca cct Thr Cys Pro Pro Cys Pro Ala Pro 55 60 ttc ctc ttc ccc cca aaa ccc aag Phe Leu Phe Pro Pro Lys Pro Lys 75 cct gag gtc aca tgc gtg gtg Pro Glu Val Thr Cys Val Val Val 90	DNA Artificial Sequence Description of Artificial Sequence: CDS (41)(871) 19 gatttg agttttaact tttagaagga ggaataa: Cys His Phe Gly Pro Leu Thr Trp Val 10 15 ggc ggc ggc ggt ggt acc tat tcc tgt Gly Gly Gly Gly Gly Thr Tyr Ser Cys 25 30 gta tgt aag cca caa ggg ggt ggg gga Val Cys Lys Pro Gln Gly Gly Gly Gly 40 45 aca tgt cca cct tgc cca gca cct gaa Thr Cys Pro Pro Cys Pro Ala Pro Glu 55 60 ttc ctc ttc ccc cca aaa ccc aag gac Phe Leu Phe Pro Pro Lys Pro Lys Asp 75 cct gag gtc aca tgc gtg gtg gtg gac Pro Glu Val Thr Cys Val Val Val Asp 90 95	DNA Artificial Sequence Description of Artificial Sequence:EMP CDS (41)(871) 19 gatttg agttttaact tttagaagga ggaataaaat tgc cac ttc ggc cca ctg act tgg gtt tgc Cys His Phe Gly Pro Leu Thr Trp Val Cys 10 15 ggc ggc ggc ggt ggt acc tat tcc tgt cat Gly Gly Gly Gly Gly Thr Tyr Ser Cys His 25 30 gta tgt aag cca caa ggg ggt ggg gga ggc Val Cys Lys Pro Gln Gly Gly Gly Gly Gly 40 45 aca tgt cca cct tgc cca gca cct gaa ctc Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu 55 60 ttc ctc ttc ccc cca aaa ccc aag gac acc Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr 75 80 cct gag gtc aca tgc gtg gtg gtg gac gtc Pro Glu Val Thr Cys Val Val Val Asp Val 90 95	DNA Artificial Sequence Description of Artificial Sequence: EMP-EMP-EMP-EMP-EMP-EMP-EMP-EMP-EMP-EMP-	B881 DNA Artificial Sequence Description of Artificial Sequence: EMP-EMP-Fc CDS (41)(871) 19 gatttg agttttaact tttagaagga ggaataaaat atg gga Met Gly	B811 DNA Artificial Sequence Description of Artificial Sequence: EMP-EMP-FC CDS (41)(871) 19 gatttg agttttaact tttagaagga ggaataaaat atg gga ggt Met Gly Gly Gly Gly Fro Leu Thr Trp Val Cys Lys Pro Gln 10 10 15 ggc ggc ggc ggt ggt acc tat tcc tgt cat ttt ggc ccg Gly Gly Gly Gly Gly Thr Tyr Ser Cys His Phe Gly Pro 25 30 35 gta tgt aag cca caa ggg ggt ggg gga ggc ggg ggg ggc ggc ggc ggc ggc	B81 DNA Artificial Sequence Description of Artificial Sequence:EMP-EMP-FC CDS (41)(871) 19 yeatting and titta act tittaga and any grad and tittaga and grad grad and any grad and tittaga and grad grad and tittaga and grad grad and tittaga and grad grad grad grad grad grad grad gra	881 DNA Artificial Sequence Description of Artificial Sequence:EMP-EMP-Fc CDS (41)(871) 19 gatting agithtaact thicagaagga ggaataaaat atg gga ggi act tac Met Gly Gly Thr Tyr 1 5 tigc cac tic ggc cca ctg act tgg git tgc aaa ccg cag ggi ggc Cys His Phe Gly Pro Leu Thr Try Val Cys Lys Pro Gln Gly Gly 10 15 20 ggc ggc ggc ggt ggi acc tat tcc tgt cat tit ggc ccg ctg acc Gly Gly Gly Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr 25 30 35 gta tgt aag cca caa ggg ggi ggi ggi ggg gga ggc ggg gg gac aaa act Val Cys Lys Pro Gln Gly Gly Gly Gly Gly Gly Gly Gly Shy Thr 40 45 50 aca tgt cca cct tgc cca gca cct gaa ctc ctg ggg gga ccg tca Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser 55 ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg atc tcc cgg Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg 75 80 cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac gaa gac cct Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro 100

105 110 115

aag	aca	aag	ccg	cgg	gag	gag	cag	tac	aac	agc	acg	tac	cgt	gtg	gtc	439
Lvs	Thr	Lvs	Pro	Ara	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	
-,-		120		•			125					130				
		120														
					a+ a	C2C	cad	asc.	taa	cta	aat	aac	ааσ	gag	tac	487
agc	gtc	CEC	acc	gee	-	vac.	Ca9	3.00	u~~	Lou	Acn	G1 v	Larg	Glu	ጥህተ	
Ser		Leu	Thr	vaı	Leu		GIN	ASD	IID	Heu		Gry	 y	Glu	-3-	
	135					140					145				•	
•																e 3 E
aag	tgc	aag	gtc	tcc	aac	aaa	gcc	ctc	cca	gcc	CCC	atc	gag	aaa	acc	535
Lvs	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	
150	_				155					160					165	
	+ - - -	222	acc	222	aaa	cad	ccc	саа	gaa	cca	cag	gtg	tac	acc	ctg	583
71.	200	1	310	Tara	614	Gln	Pro	Ara	Glu	Pro	Gln	Val	Tvr	Thr	Leu	
TIE	ser	гЛя	Ald		GIY	GIII		7	175				•	180		
				170					113							
													a+ a	200	tac	631
CCC	cca	tcc	cgg	gat	gag	ctg	acc	aag	aac	cag	gtc	agc	- CLG	acc	2	031
Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	
			185					190					195			
cto	ato	aaa	aac	ttc	tat	ccc	agc	gac	atc	gcc	gtg	gag	tgg	gag	agc	679
Len	Val	T.ve	Glv	Phe	Tvr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	
TEO	Val	200			-3-		205	•				210				
		200														
									300	200	cct	ccc	ata	cta	gac	727
aat	ggg	cag	ccg	gag	aac	aac	tac	aay	mb-	mb-	משכם	Dro	Val	1.611	gac	
Asr	Gly	r Gln	Pro	Glu	Asn			гЛя	THE	THI	225	FLO	***	200	Asp	
	215	;				220					225					
																775
tco	gad	ggc	tcc:	: ttc	ttc	ctc	tac	ago	aag	ctc	acc	gtg	gac	aag	agc	1,15
Sea	: Asr	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	
230		_			235					240)				245	
2.77	. +a	r cac	r cac	r aac	r aac	: atc	tto	: tca	tgc	tco	gtg	atg	cat	gag	gct	823
299	. m	, Ca		, 995 , G1,	, act	val	Phe	Ser	Cvs	Ser	. Val	Met	His	Glu	Ala	
AI	l tri) GII	ı Gıı						255					260)	
				250	,				2.33							
											- ~+-	, +a+		a aat	: aaa	871
ct	g ca	c aa	c cad	c tac	c acq	g cac	aaç	ago	. 650			,	. Du	ינים. יעע פ	aaa Lws	
Le	u Hi	s As	n Hi	TYI	Th	c Gli	ı Lya	s Ser	r Lev	ı sei	r re/	ı sei	. FIG	- - GT	/ Lys	
			26					270)				27!	•		
ta	atgg	atcc														881
Ca	7 7															

<210> 20 <211> 277 <212> PRT

<213> Artificial Sequence <223> Description of Artificial Sequence: EMP-EMP-Fc

<400> 20

Met Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys
1 5 10 15

Lys Pro Gln Gly Gly Gly Gly Gly Gly Gly Thr Tyr Ser Cys His
20 25 30

Phe Gly Pro Leu Thr Trp Val Cys Lys Pro Gln Gly Gly Gly Gly Gly 35 40 45

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu 50 55 60

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr 65 70 75 80

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val 85 90 95

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val 100 105 110

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser 115 120 125

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu 130 135 140

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala 145 150 155 160

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro 165 170 175

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln 180 185 190

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala 195 200 205

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr 210 215 220

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu 225 230 235 240

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser 250 245 Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser 265 Leu Ser Pro Gly Lys 275 <210> 21 <211> 884 <212> DNA <213> Artificial Sequence <220> <223> Description of Artificial Sequence:Fc-EMP-EMP <220> <221> CDS <222> (39)..(869) <400> 21 tctagatttg ttttaactaa ttaaaggagg aataacat atg gac aaa act cac aca 56 Met Asp Lys Thr His Thr tgt cca cct tgc cca gca cct gaa ctc ctg ggg gga ccg tca gtt ttc 104 Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe 20 15 10 ctc ttc ccc cca aaa ccc aag gac acc ctc atg atc tcc cgg acc cct Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro 30

aag ttc aac tgg tac gtg gac ggc gtg gag gtg cat aat gcc aag aca 248
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
55 60 65 70

50

200

gag gtc aca tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val

45

40

aag ccg cgg gag gag cag tac aac agc acg tac cgt gtg gtc agc gtc 296
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
75 80 85

				cac His												344	
aag Lys	gtc Val	tcc Ser 105	aac Asn	aaa Lys	gcc Ala	ctc Leu	cca Pro 110	gcc Ala	ccc Pro	atc Ile	gag Glu	aaa Lys 115	acc Thr	atc Ile	tcc Ser	392	
				cag Gln												440	
tcc Ser 135	cgg Arg	gat [°] Asp	g a g Glu	ctg Leu	acc Thr 140	aag Lys	aac Asn	cag Gln	gtc Val	agc Ser 145	ctg Leu	acc Thr	tgc Cys	ctg Leu	gtc Val 150	488	
aaa Lys	ggc Gly	ttc Phe	tat Tyr	ccc Pro 155	agc Ser	gac Asp	atc Ile	gcc Ala	gtg Val 160	gag Glu	tgg Trp	gag Glu	agc Ser	aat Asn 165	ggg Gly	536	
cag Gln	ccg Pro	gag Glu	aac Asn 170	aac Asn	tac Tyr	aag Lys	acc Thr	acg Thr 175	cct Pro	ccc Pro	gtg Val	ctg Leu	gac Asp 180	tcc Ser	gac Asp	584	
ggc Gly	tcc Ser	ttc Phe 185	ttc Phe	ctc Leu	tac Tyr	agc Ser	aag Lys 190	ctc Leu	acc Thr	gtg Val	gac Asp	aag Lys 195	agc Ser	agg Arg	tgg Trp	632	
cag Gln	cag Gln 200	Gly	aac Asn	gtc Val	ttc Phe	tca Ser 205	tgc Cys	tcc Ser	gtg Val	atg Met	cat His 210	Glu	gct Ala	ctg Leu	cac His	680	
aac Asn 215	His	tac Tyr	acg Thr	cag Gln	aag Lys 220	. Ser	ctc L e u	tcc Ser	ctg Leu	tct Ser 225	Pro	ggt Gly	aaa Lys	ggt Gly	gga Gly 230	728	
ggt Gly	ggt Gly	ggc Gly	gga Gly	ggt Gly 235	Thr	tac Tyr	tct Ser	tgc Cys	cac His 240	Phe	ggc Gly	cca Pro	ctg Leu	Thr 245	tgg Trp	776	
gtt Val	tgc Cys	aaa Lys	ccg Pro 250	Gln	ggt Gly	ggc Gly	ggc Gly	ggc Gly 255	Gly	ggc Gly	ggt Gly	ggt Gly	Thr	туг	tcc Ser	824	
tgt Cys	cat His	ttt Phe	Gly	c ccg / Pro	r ctg	acc Thr	tgg Trp 270	Va]	tgt Cys	aaq Lys	g cca B Pro	a caa 5 Glr 275	7 GT2	ggt Gly	ξ - Y	869	

taatctcgag gatcc

884

<210> 22

<211> 277

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence:Fc-EMP-EMP

<400> 22

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu 1 5 10 15

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu 20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser 35 40 45

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu 50 55 60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr 65 70 75 80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn 85 90 95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro 100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val 130 135 140

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val 145 150 155 160

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro 165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

195 200 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu 210 215 220

Ser Pro Gly Lys Gly Gly Gly Gly Gly Gly Gly Thr Tyr Ser Cys His 225 230 235 240

Phe Gly Pro Leu Thr Trp Val Cys Lys Pro Gln Gly Gly Gly Gly 245 250 255

Gly Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys
260 265 270

Lys Pro Gln Gly Gly 275

<210> 23

<211> 1545

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:pAMG216

<400> 23

cgtaacgtat gcatggtctc cccatgcgag agtagggaac tgccaggcat caaataaaac 60 gaaaggctca gtcgaaagac tgggcctttc gttttatctg ttgtttgtcg gtgaacgctc 120 tcctgagtag gacaaatccg ccgggagcgg atttgaacgt tgcgaagcaa cggcccggag 180 ggtggcgggc aggacgcccg ccataaactg ccaggcatca aattaagcag aaggccatcc 240 tgacggatgg cctttttgcg tttctacaaa ctcttttgtt tatttttcta aatacattca 300 aatatggacg tcgtacttaa cttttaaagt atgggcaatc aattgctcct gttaaaattg 360 ctttagaaat actttggcag cggtttgttg tattgagttt catttgcgca ttggttaaat 420 ggaaagtgac cgtgcgctta ctacagccta atatttttga aatatcccaa gagctttttc 480 cttcgcatgc ccacgctaaa cattctttt ctcttttggt taaatcgttg tttgatttat 540 tatttgctat atttatttt cgataattat caactagaga aggaacaatt aatggtatgt 600 tcatacacgc atgtaaaaat aaactatcta tatagttgtc tttctctgaa tgtgcaaaac 660 taagcattcc gaagccatta ttagcagtat gaatagggaa actaaaccca gtgataagac 720 ctgatgattt cgcttcttta attacatttg gagatttttt atttacagca ttgttttcaa 780 atatattcca attaatcggt gaatgattgg agttagaata atctactata ggatcatatt 840 ttattaaatt agcgtcatca taatattgcc tccatttttt agggtaatta tccagaattg 900 aaatatcaga tttaaccata gaatgaggat aaatgatcgc gagtaaataa tattcacaat 960 gtaccatttt agtcatatca gataagcatt gattaatatc attattgctt ctacaggctt 1020 taattttatt aattattctg taagtgtcgt cggcatttat gtctttcata cccatctctt 1080 tatecttace tattgtttgt egeaagtttt gegtgttata tateattaaa aeggtaatag 1140 attgacattt gattctaata aattggattt ttgtcacact attatatcgc ttgaaataca 1200

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attgtttaac ataagtacct gtaggatcgt acaggtttac gcaagaaaat ggtttgttat 1260
agtcgattaa tcgatttgat tctagatttg ttttaactaa ttaaaggagg aataacatat 1320
ggttaacgcg ttggaattcg agctcactag tgtcgacctg Cagggtacca tggaagctta 1380
ctcgaggatc cgcggaaaga agaagaagaa gaagaaagcc cgaaaggaag ctgagttggc 1440
tgctgccacc gctgagcaat aactagcata accccttggg gcctctaaac gggtcttgag 1500
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<210> 24
<211> 14
<212> PRT
<213> Artificial Sequence
.<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 24
Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Lys Ala
                                     10
                  5
<210> 25
<211> 14
<212> PRT
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<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 25
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Ile Glu Gly Pro Thr Leu Arg Glu Trp Leu Ala Ala Arg Ala 10 5

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<210> 26
<211> 29
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
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<220>

<223> At position 15, Xaa=a linker sequence of 1 to 20 amino acids

<400> 26

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Xaa Ile 1 5 10 15

Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
20 25

<210> 27

<211> 29

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TPO-MIMETIC PEPTIDE

<220>

<223> At position 15, Xaa=a linker sequence of 1 to 20 amino acids

<400> 27

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Lys Ala Xaa Ile 1 5 10 15

Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Lys Ala 20 25

<210> 28

<211> 29

<212> PRT

<213> Artificial Sequence

<220>

<220>

<223> At position 9 disulfide linkage with residue 24

<220>

<223> At position 24 disulfide linkage with residue 9

<400> 28 Ile Glu Gly Pro Thr Leu Arg Gln Cys Leu Ala Ala Arg Ala Xaa Ile 5 10 Glu Gly Pro Thr Leu Arg Gln Cys Leu Ala Ala Arg Ala 25 <210> 29 <211> 31 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: TPO-MIMETIC PEPTIDE <220> <223> At position 16 bromoacetyl group linked to sidechain <400> 29 Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Xaa Lys 5 Xaa Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala 25 20 <210> 30 <211> 31 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: TPO-MIMETIC PEPTIDE <220> <223> At position 16 polyethylene glycol linked to sidechain

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Xaa Lys

10

15

<400> 30 ...

1

Xaa Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
20 25 30

<210> 31

<211> 29

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TPO-MIMETIC PEPTIDE

<220>

<223> At position 9 disulfide bond to residue 9 of a separate identical sequence

<400> 31

Ile Glu Gly Pro Thr Leu Arg Gln Cys Leu Ala Ala Arg Ala Xaa Ile 1 5 10 15

Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
20 25

<210> 32

<211> 29

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TPO-MIMETIC PEPTIDE

<220>

<223> At position 24 disulfide bond to residue 9 of a separate identical sequence

<400> 32

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Xaa Ile 1 5 10 15

Glu Gly Prö Thr Leu Arg Gln Cys Leu Ala Ala Arg Ala
20 25

```
<210> 33
<211> 9
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:TPO-MIMETIC
      PEPTIDE
<400> 33
Val Arg Asp Gln Ile Xaa Xaa Xaa Leu
           5
<210> 34
<211> 6
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 34
Thr Leu Arg Glu Trp Leu
<210> 35
<211> 10
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 35
Gly Arg Val Arg Asp Gln Val Ala Gly Trp
                 5
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<210> 36

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<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 36
Gly Arg Val Lys Asp Gln Ile Ala Gln Leu
                  5
<210> 37
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:Description of
      Artificial SequenceTPO-MIMETIC PEPTIDE
<400> 37
Gly Val Arg Asp Gln Val Ser Trp Ala Leu
                  5
<210> 38
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 38
Glu Ser Val Arg Glu Gln Val Met Lys Tyr
  1
                   5
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<210> 39 <211> 10 <212> PRT

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<220>
 <223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
 <400> 39
 Ser Val Arg Ser Gln Ile Ser Ala Ser Leu
                  5
<210> 40
<211> 10
 <212> PRT
 <213> Artificial Sequence
<220>
 <223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
 <400> 40
 Gly Val Arg Glu Thr Val Tyr Arg His Met
                  5
 <210> 41
 <211> 11
 <212> PRT
<213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: INTEGRIN
      BINDING PEPTIDE
 Gly Val Arg Glu Val Ile Val Met His Met Leu
 <210> 42
 <211> 11
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: TPO-MIMETIC
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PEPTIDE

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<400> 42
Gly Arg Val Arg Asp Gln Ile Trp Ala Ala Leu
1 5 10
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<210> 43 <211> 11 <212> PRT

<213> Artificial Sequence

<220>

<400> 43
Ala Gly Val Arg Asp Gln Ile Leu Ile Trp Leu

1 5 10

<210> 44 <211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC PEPTIDE

<400> 44

Gly Arg Val Arg Asp Gln Ile Met Leu Ser Leu

1 5 10

<210> 45

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<400> 45

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Gly Arg Val Arg Asp Gln Ile Xaa Xaa Xaa Leu
                   5
<210> 46
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 46
Cys Thr Leu Arg Gln Trp Leu Gln Gly Cys
                   5
 <210> 47
 <211> 10
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: TPO-MIMETIC
       PEPTIDE
 <400> 47
 Cys Thr Leu Gln Glu Phe Leu Glu Gly Cys
                  5
 <210> 48
 <211> 10
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: TPO-MIMETIC
       PEPTIDE
 <400> 48
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10

Cys Thr Arg Thr Glu Trp Leu His Gly Cys

5

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<210> 49
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 49
Cys Thr Leu Arg Glu Trp Leu His Gly Gly Phe Cys
                                     10
                  5
<210> 50
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:Fc-TMP
<400> 50
Cys Thr Leu Arg Glu Trp Val Phe Ala Gly Leu Cys
                  5
<210> 51
<211> 13
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:Fc-TMP
<400> 51
Cys Thr Leu Arg Gln Trp Leu Ile Leu Leu Gly Met Cys
                   5
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<210> 52 ···· <211> 14 <212> PRT

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<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 52
Cys Thr Leu Ala Glu Phe Leu Ala Ser Gly Val Glu Gln Cys
                  5
                                     10
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<210> 53
<211> 14
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:Fc-TMP
<400> 53
Cys Ser Leu Gln Glu Phe Leu Ser His Gly Gly Tyr Val Cys
                 5
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<210> 54
<211> 14
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:Fc-TMP
<400> 54
Cys Thr Leu Arg Glu Phe Leu Asp Pro Thr Thr Ala Val Cys
                                     10
  1
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<210> 55
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:TPO-MIMETIC PEPTIDE

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<400> 55
Cys Thr Leu Lys Glu Trp Leu Val Ser His Glu Val Trp Cys
                  5
<210> 56
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 56
Cys Thr Leu Arg Glu Trp Leu Xaa Xaa Cys
                  5
 1
<210> 57
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 57
Cys Thr Leu Arg Glu Trp Leu Xaa Xaa Xaa Cys
                                      10
                   5
<210> 58
<211> 12
<212> PRT
<213> Artificial Sequence
 <223> Description of Artificial Sequence: TPO-MIMETIC
       PEPTIDE
 <400> 58
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Cys Thr Leu Arg Glu Trp Leu Xaa Xaa Xaa Xaa Cys

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1 5 10

<210> 59

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<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TPO-MIMETIC
 PEPTIDE

<400> 59

Cys Thr Leu Arg Glu Trp Leu Xaa Xaa Xaa Xaa Xaa Cys

<210> 60

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TPO-MIMETIC
 PEPTIDE

<400> 60

Cys Thr Leu Arg Glu Trp Leu Xaa Xaa Xaa Xaa Xaa Cys

<210> 61

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC PEPTIDE

<400> 61

Arg Glu Gly Pro Thr Leu Arg Gln Trp Met

1 5 10

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<210> 62
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 62
Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala
                 5
<210> 63
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 63
Glu Arg Gly Pro Phe Trp Ala Lys Ala Cys
                5
<210> 64
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 64
Arg Glu Gly Pro Arg Cys Val Met Trp Met
                  5
. . 1
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<210> 65 <211> 14

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<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 65
Cys Gly Thr Glu Gly Pro Thr Leu Ser Thr Trp Leu Asp Cys
                5
                                   10
<210> 66
<211> 14
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 66
Cys Glu Gln Asp Gly Pro Thr Leu Leu Glu Trp Leu Lys Cys
 1
                 5
                                    10
<210> 67
<211> 14
<212> PRT
<213> Artificial Sequence
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```
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
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<400> 67 Cys Glu Leu Val Gly Pro Ser Leu Met Ser Trp Leu Thr Cys 10 5

<210> 68 <211> 14 <212> PRT ... <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TPO-MIMETIC PEPTIDE

<400> 68

Cys Leu Thr Gly Pro Phe Val Thr Gln Trp Leu Tyr Glu Cys
1 5 10

<210> 69

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TPO-MIMETIC PEPTIDE

<400> 69

Cys Arg Ala Gly Pro Thr Leu Leu Glu Trp Leu Thr Leu Cys
1 5 10

<210> 70

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<400> 70

Cys Ala Asp Gly Pro Thr Leu Arg Glu Trp Ile Ser Phe Cys
1 5 10

<210> 71

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

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<400> 71
Cys Xaa Glu Gly Pro Thr Leu Arg Glu Trp Leu Xaa Cys
                                     10
                  5
<210> 72
<211> 14
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
<400> 72
Cys Xaa Xaa Glu Gly Pro Thr Leu Arg Glu Trp Leu Xaa Cys
                                     10
 1
                  5
<210> 73
<211> 14
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
Cys Xaa Glu Gly Pro Thr Leu Arg Glu Trp Leu Xaa Xaa Cys
                  5
  1
<210> 74
<211> 15
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDE
Cys Xaa Xaa Glu Gly Pro Thr Leu Arg Glu Trp Leu Xaa Xaa Cys
```

1 5 10 15

<210> 75

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC PEPTIDE

<400> 75

Gly Gly Cys Thr Leu Arg Glu Trp Leu His Gly Gly Phe Cys Gly Gly

1 5 10 15

<210> 76

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC PEPTIDE

<400> 76

Gly Gly Cys Ala Asp Gly Pro Thr Leu Arg Glu Trp Ile Ser Phe Cys
1 5 10 15

Gly Gly

<210> 77

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC PEPTIDE

<400> 77

Gly Asn Ala Asp Gly Pro Thr Leu Arg Gln Trp Leu Glu Gly Arg Arg

1 5 10 15

Pro Lys Asn

<210> 78

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<400> 78

Leu Ala Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu His Gly Asn Gly

1 5 10 15

Arg Asp Thr

<210> 79

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<400> 79

His Gly Arg Val Gly Pro Thr Leu Arg Glu Trp Lys Thr Gln Val Ala 1 5 10 15

Thr Lys Lys

<210> 80

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC PEPTIDE

<400> 80

Thr Ile Lys Gly Pro Thr Leu Arg Gln Trp Leu Lys Ser Arg Glu His 1 5 10 15

Thr Ser

<210> 81

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TPO-MIMETIC
 PEPTIDE

<400> 81

Ile Ser Asp Gly Pro Thr Leu Lys Glu Trp Leu Ser Val Thr Arg Gly
1 5 10 15

Ala Ser

<210> 82

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TPO-MIMETIC
 PEPTIDE

<400> 82

Ser Ile Glu Gly Pro Thr Leu Arg Glu Trp Leu Thr Ser Arg Thr Pro 1 5 10 15

His Ser

<210> 84 <211> 28 <212> PRT <213> Artificial Sequence

Cys Xaa Xaa Gly Pro Xaa Thr Trp Xaa Cys Xaa Pro 20 25

<210> 85 <211> 29 <212> PRT <213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: EPO-MIMETIC PEPTIDE

<220>
<223> At position 15, Xaa=a linker sequence of 1 to 20 amino acids

<400> 85

Tyr Xaa Cys Xaa Xaa Gly Pro Xaa Thr Trp Xaa Cys Xaa Pro Xaa Tyr 1 5 10 15

Xaa Cys Xaa Xaa Gly Pro Xaa Thr Trp Xaa Cys Xaa Pro
20 25

<210> 86

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<220>

<223> At position 15 linked through epsilon amine to lysyl, which is linked to a separate identical sequence through that sequence's alpha amine

<400> 86

Tyr Xaa Cys Xaa Xaa Gly Pro Xaa Thr Trp Xaa Cys Xaa Pro 1 5 10

<210> 87

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<400> 87

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly

20

<210> 88

<211> 20

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<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EPO-MIMETIC
     PEPTIDE
<400> 88
Gly Gly Asp Tyr His Cys Arg Met Gly Pro Leu Thr Trp Val Cys Lys
                5 .
                                  10
Pro Leu Gly Gly
            20
<210> 89
<211> 20
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: EPO-MIMETIC
     PEPTIDE
<400> 89
Gly Gly Val Tyr Ala Cys Arg Met Gly Pro Ile Thr Trp Val Cys Ser
                                    10
Pro Leu Gly Gly
             20
<210> 90
<211> 20
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EPO-MIMETIC
      PEPTIDE
<400> 90
Val Gly Asn Tyr Met Cys His Phe Gly Pro Ile Thr Trp Val Cys Arg
 1 ... 5
                                     10
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Pro Gly Gly Gly

20

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<210> 91
<211> 20
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EPO-MIMETIC
      PEPTIDE
<400> 91
Gly Gly Leu Tyr Leu Cys Arg Phe Gly Pro Val Thr Trp Asp Cys Gly
                                    10
        5
Tyr Lys Gly Gly
             20
<210> 92
<211> 40
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EPO-MIMETIC
      PEPTIDE
Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
                                                        15
                  5
 1
Pro Gln Gly Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr
                                 25
             20
 Trp Val Cys Lys Pro Gln Gly Gly
         35
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<210> 93 <211> 41 <212> PRT ... <213> Artificial Sequence <220>

<223> Description of Artificial Sequence: EPO-MIMETIC PEPTIDE

<220>

<223> At position 21, Xaa=a linker sequence of 1 to 20 amino acids

<400> 93

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly Kaa Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu 20 25 30

Thr Trp Val Cys Lys Pro Gln Gly Gly 35 40

<210> 94

<211> 23

<212> PRT

<213> Artificial Sequence

<220>

<400> 94

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly Ser Ser Lys
20

<210> 95

<211> 46

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TPO-MIMETIC
 PEPTIDE

<400> 95

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys

1 5 10 15

Pro Gln Gly Gly Ser Ser Lys Gly Gly Thr Tyr Ser Cys His Phe Gly
20 25 30

Pro Leu Thr Trp Val Cys Lys Pro Gln Gly Gly Ser Ser Lys 35 40 45

<210> 96

<211> 47

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TPO-MIMETIC PEPTIDE

<220>

<223> At position 24, Xaa=a linker sequence of 1 to 20 amino acids

<400> 96

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly Ser Ser Lys Xaa Gly Gly Thr Tyr Ser Cys His Phe 20 25 30

Gly Pro Leu Thr Trp Val Cys Lys Pro Gln Gly Gly Ser Ser Lys 35 40 45

<210> 97

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:EPO-MIMETIC
 PEPTIDE

<220>

<223> At position 22 linked through epsilon amine to lysyl, which is linked to a separate identical

sequence through that sequence's alpha amine

<400> 97

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly Ser Ser 20

<210> 98

<211> 23

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EPO-MIMETIC PEPTIDE

<220>

<223> At position 23 biotin linked to the sidechain through a linker

<400> 98

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly Ser Ser Lys
20

<210> 99

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:G-CSF MIMETIC PEPTIDE

<220>

<223> At position 4 disulfide bond to residue 4 of a separate identical sequence

<400> 99

Glu Glu Asp Cys Lys

1 5

<210> 100

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:G-CSF MIMETIC
 PEPTIDE

<220>

<223> At position 4, Xaa is an isoteric ethylene spacer linked to a separate identical sequence

<400> 100

Glu Glu Asp Xaa Lys

1

<210> 101

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:G-CSF MIMETIC
 PEPTIDE

<220>

<223> At position 1, Xaa is a pyroglutamic acid residue

<220>

<223> At position 4, Xaa is an isoteric ethylene spacer linked to a separate identical sequence

<400> 101

Xaa Glu Asp Xaa Lys

1

5

<210> 102 ...

<211> 5

<212> PRT

```
<213> Artificial Sequence
```

<220>

<223> Description of Artificial Sequence: EPO-MIMETIC PEPTIDE

<220>

<223> At position 1, Xaa is a picolinic acid residue

<220>

<223> At position 4, Xaa is an isoteric ethylene spacer linked to a separate identical sequence

<400> 102

Xaa Ser Asp Xaa Lys

1

5

<210> 103

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EPO-MIMETIC PEPTIDE

<220>

<223> At position 6, Xaa=a linker sequence of 1 to 20 amino acids

<400> 103

Glu Glu Asp Cys Lys Xaa Glu Glu Asp Cys Lys 1 5 10

<210> 104

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:EPO-MIMETIC
 PEPTIDE

<220>

```
<223> At position 6, Xaa=a linker sequence of 1 to 20
      amino acids
<400> 104
Glu Glu Asp Xaa Lys Xaa Glu Glu Asp Xaa Lys
<210> 105
<211> 6
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: ANTIVIRAL (HBV)
     PEPTIDE
<400> 105
Leu Leu Gly Arg Met Lys
<210> 106
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TNF-ANTAGONIST
      PEPTIDE
<400> 106
Tyr Cys Phe Thr Ala Ser Glu Asn His Cys Tyr
                 5
 1
<210> 107
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TNF-ANTAGONIST
      PEPTIDE
```

```
<400> 107
Tyr Cys Phe Thr Asn Ser Glu Asn His Cys Tyr
                                     10
                 5
<210> 108
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:TNF-ANTAGONIST
      PEPTIDE
<400> 108
Tyr Cys Phe Thr Arg Ser Glu Asn His Cys Tyr
                5
<210> 109
<211> 9
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: TNF-ANTAGONIST
      PEPTIDE
<400> 109
Phe Cys Ala Ser Glu Asn His Cys Tyr
<210> 110
<211> 9
<212> PRT
<213> Artificial Sequence
<220>
```

<400> 110 ...
Tyr Cys Ala Ser Glu Asn His Cys Tyr
1 5

PEPTIDE

<223> Description of Artificial Sequence: TNF-ANTAGONSIT

```
<210> 111
<211> 9
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: TNF-ANTAGONIST
      PEPTIDE
<400> 111
Phe Cys Asn Ser Glu Asn His Cys Tyr
<210> 112
<211> 9
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TNF-ANTAGONIST
      PEPTIDE
<400> 112
Phe Cys Asn Ser Glu Asn Arg Cys Tyr
                  5
<210> 113
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:TNF-ANTAGONIST
      PEPTIDE
<400> 113
Phe Cys Asn Ser Val Glu Asn Arg Cys Tyr
                 5
```

```
<210> 114
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TNF-ANTAGONIST
<400> 114
Tyr Cys Ser Gln Ser Val Ser Asn Asp Cys Phe
                5
<210> 115
<211> 9
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TNF-ANTAGONIST
<400> 115
Phe Cys Val Ser Asn Asp Arg Cys Tyr
                 5
<210> 116
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TNF-ANTAGONIST
      PEPTIDE
<400> 116
Tyr Cys Arg Lys Glu Leu Gly Gln Val Cys Tyr
```

<210> 117 ... <211> 9 <212> PRT

5

```
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TNF-ANTAGONIST
<400> 117
Tyr Cys Lys Glu Pro Gly Gln Cys Tyr
                  5
<210> 118
<211> 9
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TNF-ANTAGONIST
<400> 118
Tyr Cys Arg Lys Glu Met Gly Cys Tyr
                  5
<210> 119
<211> 9
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TNF-ANTAGONIST
<400> 119
Phe Cys Arg Lys Glu Met Gly Cys Tyr
<210> 120
<211> 9
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: TNF-ANTAGONIST
<400> 120
```

```
Tyr Cys Trp Ser Gln Asn Leu Cys Tyr
                   5
 <210> 121
<211> 10
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: TNF-ANTAGONIST
 <400> 121
 Tyr Cys Glu Leu Ser Gln Tyr Leu Cys Tyr
                  5
 <210> 122
 <211> 9
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: TNF-ANTAGONIST
  <400> 122
  Tyr Cys Trp Ser Gln Asn Tyr Cys Tyr
                    5
  <210> 123
  <211> 9
  <212> PRT
  <213> Artificial Sequence
  <220>
  <223> Description of Artificial Sequence: TNF-ANTAGONIST
  <400> 123
  Tyr Cys Trp Ser Gln Tyr Leu Cys Tyr
```

<210> 124

<211> 37

<212> PRT

<213> Artificial Sequence

<220>

<400> 124

Xaa Xaa Xaa Xaa Xaa 35

<210> 125

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:CTLA4-MIMETIC
 PEPTIDE

<400> 125

Gly Phe Val Cys Ser Gly Ile Phe Ala Val Gly Val Gly Arg Cys
1 5 10 15

<210> 126

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<400> 126

Ala Pro Gly Val Arg Leu Gly Cys Ala Val Leu Gly Arg Tyr Cys
10
15

```
<210> 127
<211> 27
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:C3B ANTAGONIST
<400> 127
Ile Cys Val Val Gln Asp Trp Gly His His Arg Cys Thr Ala Gly His
                                     10
                  5
Met Ala Asn Leu Thr Ser His Ala Ser Ala Ile
                                  25
             20
<210> 128
<211> 13
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: C3B ANTAGONIST
       PEPTIDE
 <400> 128
 Ile Cys Val Val Gln Asp Trp Gly His His Arg Cys Thr
                                      10
 <210> 129
 <211> 11
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: C3B ANTAGONIST
       PEPTIDE
 <400> 129
 Cys Val Val Gln Asp Trp Gly His His Ala Cys
```

5

```
<210> 130
<211> 6
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:MDM/HDM
     ANTAGONIST PEPTIDE
<400> 130
Thr Phe Ser Asp Leu Trp
<210> 131
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:MDM/HDM
      ANTAGONIST PEPTIDE
<400> 131
Gln Glu Thr Phe Ser Asp Leu Trp Lys Leu Leu Pro
                  5
<210> 132
 <211> 12
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence:MDM/HDM
       ANTAGONIST PEPTIDE
 <400> 132
 Gln Pro Thr Phe Ser Asp Leu Trp Lys Leu Leu Pro
```

5

<210> 133 <211> 12

1

10

```
<212> PRT
```

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:MDM/HDM ANTAGONIST PEPTIDE

<400> 133

Gln Glu Thr Phe Ser Asp Tyr Trp Lys Leu Leu Pro
1 5 10

<210> 134

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:MDM/HDM ANTAGONIST PEPTIDE

<400> 134

Gln Pro Thr Phe Ser Asp Tyr Trp Lys Leu Leu Pro 1 5 10

<210> 135

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:MDM/HDM ANTAGONIST PEPTIDE

<400> 135

Met Pro Arg Phe Met Asp Tyr Trp Glu Gly Leu Asn 1 5 10

<210> 136

<211> 12

<212> PRT...

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: C3B ANTAGONIST

<400> 136

Val Gln Asn Phe Ile Asp Tyr Trp Thr Gln Gln Phe 5

<210> 137

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:MDM/HDM ANTAGONIST PEPTIDE

<400> 137

Thr Gly Pro Ala Phe Thr His Tyr Trp Ala Thr Phe 10

<210> 138

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:MDM/HDM ANTAGONIST PEPTIDE

<400> 138

Ile Asp Arg Ala Pro Thr Phe Arg Asp His Trp Phe Ala Leu Val 10 5

<210> 139

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:MDM/HDM ANTAGONIST PEPTIDE

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```
WO 00/24782
<400> 139
Pro Arg Pro Ala Leu Val Phe Ala Asp Tyr Trp Glu Thr Leu Tyr
                                     10
                  5
<210> 140
<211> 15
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:MDM/HDM
      ANTAGONIST PEPTIDE
<400> 140
Pro Ala Phe Ser Arg Phe Trp Ser Asp Leu Ser Ala Gly Ala His
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<210> 141

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:MDM/HDM ANTAGONIST PEPTIDE

<400> 141

Pro Ala Phe Ser Arg Phe Trp Ser Lys Leu Ser Ala Gly Ala His 10 5 1

<210> 142

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:MDM/HDM 0 ANTAGONIST PEPTIDE

<400> 142

Pro Xaa Phe Xaa Asp Tyr Trp Xaa Xaa Leu 5

```
<210> 143
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:MDM/HDM
      ANTAGONIST PEPTIDE
<400> 143
Gln Glu Thr Phe Ser Asp Leu Trp Lys Leu Leu Pro
                  5
                                    10
<210> 144
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:MDM/HDM
      ANTAGONIST PEPTIDE
<400> 144
Gln Pro Thr Phe Ser Asp Leu Trp Lys Leu Leu Pro
  1
                  5
<210> 145
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:MDM/HDM
      ANTAGONIST PEPTIDE
<400> 145
Gin Glu Thr Phe Ser Asp Tyr Trp Lys Leu Leu Pro
                                    10
                 5
```

```
<210> 146
```

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:MDM/HDM ANTAGONIST PEPTIDE

<400> 146

Gln Pro Thr Phe Ser Asp Tyr Trp Lys Leu Leu Pro
1 5 10

<210> 147

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SELECTIN ANTAGONIST PEPTIDE

<400> 147

Asp Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys

1 5 10

<210> 148

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SELECTIN ANTAGONIST PEPTIDE

<400> 148

Asp Ile Thr Trp Asp Glu Leu Trp Lys Ile Met Asn 1 5 10

<210> 149 ---

<211> 12

<212> PRT

```
<213> Artificial Sequence
```

<220>

<223> Description of Artificial Sequence: SELECTIN ANTAGONIST PEPTIDE

<400> 149

Asp Tyr Thr Trp Phe Glu Leu Trp Asp Met Met Gln 1 5 10

<210> 150

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SELECTIN ANTAGONIST PEPTIDE

<400> 150

Gln Ile Thr Trp Ala Gln Leu Trp Asn Met Met Lys

1 5 10

<210> 151

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:MDM/HDM ANTAGONIST PEPTIDE

<400> 151

Asp Met Thr Trp His Asp Leu Trp Thr Leu Met Ser

1 5 10

<210> 152

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:MDM/HDM ANTAGONIST PEPTIDE

<400> 152

Asp Tyr Ser Trp His Asp Leu Trp Glu Met Met Ser

1 5 10

<210> 153

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:MDM/HDM ANTAGONIST PEPTIDE

<400> 153

Glu Ile Thr Trp Asp Gln Leu Trp Glu Val Met Asn
1 5 10

<210> 154

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:MDM/HDM ANTAGONIST PEPTIDE

<400> 154

His Val Ser Trp Glu Gln Leu Trp Asp Ile Met Asn
1 5 10

<210> 155

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SELECTIN ANTAGONIST PEPTIDE

<400> 155
His Ile Thr Trp Asp Gln Leu Trp Arg Ile Met Thr
1 5 10

<210> 156

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SELECTIN ANTAGONIST PEPTIDE

<400> 156

Arg Asn Met Ser Trp Leu Glu Leu Trp Glu His Met Lys
1 5 10

<210> 157

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SELECTIN

<400> 157

Ala Glu Trp Thr Trp Asp Gln Leu Trp His Val Met Asn Pro Ala Glu

1 5 10 15

Ser Gln

<21,0> 158

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SELECTIN

<400> 158

His Arg Ala Glu Trp Leu Ala Leu Trp Glu Gln Met Ser Pro

1 5 10

<210> 159

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SELECTIN ANTAGONIST PEPTIDE

<400> 159

Lys Lys Glu Asp Trp Leu Ala Leu Trp Arg Ile Met Ser Val 1 5 10

<210> 160

<211> 11

<212> PRT

<213> Artificial Sequence

<2205

<223> Description of Artificial Sequence: SELECTIN

<400> 160

Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys
1 5 10

<210> 161

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SELECTIN

<400> 161

Asp Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys
1 5 10

<210> 162

```
<211> 12
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: SELECTIN
<400> 162
Asp Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys
                 5
<210> 163
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SELECTIN
      ANTAGONIST PEPTIDE
<400> 163
Asp Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys
                 5
<210> 164
<211> 13
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: CALMODULIN
      ANTAGONIST PEPTIDE
<400> 164
Ser Cys Val Lys Trp Gly Lys Lys Glu Phe Cys Gly Ser
                 5
<210> 165
<211> 12
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<212> PRT ...

<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence:CALMODULIN
<400> 165
Ser Cys Trp Lys Tyr Trp Gly Lys Glu Cys Gly Ser
                 5
<210> 166
<211> 13
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:CALMODULIN
      ANTAGONIST PEPTIDE
<400> 166
Ser Cys Tyr Glu Trp Gly Lys Leu Arg Trp Cys Gly Ser
                  5
                                     10
<210> 167
<211> 13
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: CALMODULIN
      ANTAGONIST PEPTIDE
<400> 167
Ser Cys Leu Arg Trp Gly Lys Trp Ser Asn Cys Gly Ser
                  5
<210> 168
<211> 13
<212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: CALMODULIN
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ANTAGONIST PEPTIDE

```
<400> 168
Ser Cys Trp Arg Trp Gly Lys Tyr Gln Ile Cys Gly Ser
                 5
<210> 169
<211> 13
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: CALMODULIN
     ANTAGONIST PEPTIDE
<400> 169
Ser Cys Val Ser Trp Gly Ala Leu Lys Leu Cys Gly Ser
      5
<210> 170
<211> 13
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence:CALMODULIN
      ANTAGONIST PEPTIDE
<400> 170
Ser Cys Ile Arg Trp Gly Gln Asn Thr Phe Cys Gly Ser
                 5
<210> 171
<211> 13
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: CALMODULIN
      ANTAGONIST PEPTIDE
 <400> 171
```

10

Ser Cys Trp Gln Trp Gly Asn Leu Lys Ile Cys Gly Ser

```
<210> 172
 <211> 13
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence:CALMODULIN
       ANTAGONIST PEPTIDE
 <400> 172
 Ser Cys Val Arg Trp Gly Gln Leu Ser Ile Cys Gly Ser
                   5
 <210> 173
 <211> 21
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: CALMODULIN
       ANTAGONIST PEPTIDE
  <400> 173
 Leu Lys Lys Phe Asn Ala Arg Arg Lys Leu Lys Gly Ala Ile Leu Thr
                                     10
  Thr Met Leu Ala Lys
               20
  <210> 174
  <211> 18
  <212> PRT
  <213> Artificial Sequence
  <220>
  <223> Description of Artificial Sequence:CALMODULIN
  <400> 174
  Arg Arg Trp Lys Lys Asn Phe Ile Ala Val Ser Ala Ala Asn Arg Phe
                                       10
                    5
```

Lys Lys

<210> 175

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: CALMODULIN

<400> 175

Arg Lys Trp Gln Lys Thr Gly His Ala Val Arg Ala Ile Gly Arg Leu 10

Ser Ser

<210> 176

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: CALMODULIN ANTAGONIST PEPTIDE

<400> 176

Ile Asn Leu Lys Ala Leu Ala Ala Leu Ala Lys Lys Ile Leu 10 5

<210> 177

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: CALMODULIN ANTAGONIST PEPTIDE

<400> 177

Lys Ile Trp Ser Ile Leu Ala Pro Leu Gly Thr Thr Leu Val Lys Leu

1 5 10 . 15

Val Ala

<210> 178

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:CALMODULIN
ANTAGONIST PEPTIDE

<400> 178

Leu Lys Lys Leu Leu Lys Leu Leu Lys Leu Leu Lys Leu 1 5 10

<210> 179

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:CALMODULIN ANTAGONIST PEPTIDE

<400> 179

Leu Lys Trp Lys Lys Leu Leu Lys Leu Lys Lys Leu Leu Lys Lys 1 5 10 15

Leu Leu

<210> 180

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:CALMODULIN ANTAGONIST PEPTIDE

```
<400> 180
Ala Glu Trp Pro Ser Leu Thr Glu Ile Lys Thr Leu Ser His Phe Ser
                                    10
Val
<210> 181
<211> 17
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: CALMODULIN
      ANTAGONIST PEPTIDE
<400> 181
Ala Glu Trp Pro Ser Pro Thr Arg Val Ile Ser Thr Thr Tyr Phe Gly
                             . 10
Ser
<210> 182
<211> 17
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:CALMODULIN
      ANTAGONIST PEPTIDE
Ala Glu Leu Ala His Trp Pro Pro Val Lys Thr Val Leu Arg Ser Phe
                                                        15
Thr
```

<210> 183 <211> 17

```
<212> PRT
    <213> Artificial Sequence
    <220>
    <223> Description of Artificial Sequence:CALMODULIN
       ANTAGONIST PEPTIDE
    <400> 183
    Ala Glu Gly Ser Trp Leu Gln Leu Leu Asn Leu Met Lys Gln Met Asn
                                        10
    Asn
    <210> 184
~~~<211> 10
    <212> PRT
    <213> Artificial Sequence
     <220>
     <223> Description of Artificial Sequence:CALMODULIN
          ANTAGONIST PEPTIDE
     <400> 184
     Ala Glu Trp Pro Ser Leu Thr Glu Ile Lys
                     5
     <210> 185
     <211> 27
     <212> PRT
     <213> Artificial Sequence
     <220>
     <223> Description of Artificial
           Sequence: VINCULIN-BINDING PEPTIDE
     Ser Thr Gly Gly Phe Asp Asp Val Tyr Asp Trp Ala Arg Gly Val Ser
                                          10
                       5
```

· 25

Ser Ala Leu Thr Thr Thr Leu Val Ala Thr Arg

20

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10

WO 00/24782 <210> 186 <211> 27 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: VINCULIN-BINDING PEPTIDE <400> 186 Ser Thr Gly Gly Phe Asp Asp Val Tyr Asp Trp Ala Arg Arg Val Ser Ser Ala Leu Thr Thr Thr Leu Val Ala Thr Arg 20 <210> 187 <211> 30 <212> PRT <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: VINCULIN BINDING PEPTIDE

<400> 187

Ser Arg Gly Val Asn Phe Ser Glu Trp Leu Tyr Asp Met Ser Ala Ala 10

Met Lys Glu Ala Ser Asn Val Phe Pro Ser Arg Arg Ser Arg · 25 20

<210> 188

<211> 30

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: VINCULIN BINDING PEPTIDE

<400> 188

Ser Ser Gln Asn Trp Asp Met Glu Ala Gly Val Glu Asp Leu Thr Ala

1 5 10 15

Ala Met Leu Gly Leu Leu Ser Thr Ile His Ser Ser Ser Arg
20 25 30

<210> 189

<211> 31

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VINCULIN
BINDING PEPTIDE

<400> 189

Ser Ser Pro Ser Leu Tyr Thr Gln Phe Leu Val Asn Tyr Glu Ser Ala 1 5 10 15

Ala Thr Arg Ile Gln Asp Leu Leu Ile Ala Ser Arg Pro Ser Arg 20 25 30

<210> 190

<211> 31

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VINCULIN
BINDING PEPTIDE

<400> 190

Ser Ser Thr Gly Trp Val Asp Leu Leu Gly Ala Leu Gln Arg Ala Ala 1 5 10 15

Asp Ala Thr Arg Thr Ser Ile Pro Pro Ser Leu Gln Asn Ser Arg
20 25 30

<210> 191

<211> 18

<212> PRT ...

<213> Artificial Sequence

```
<220>
<223> Description of Artificial Sequence:VINCULIN
      BINDING PEPTIDE
<400> 191
Asp Val Tyr Thr Lys Lys Glu Leu Ile Glu Cys Ala Arg Arg Val Ser
                                   10
Glu Lys
<210> 192
<211> 22
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:C4BP-BINDING
      PEPTIDE
<400> 192
Glu Lys Gly Ser Tyr Tyr Pro Gly Ser Gly Ile Ala Gln Phe His Ile
                5
Asp Tyr Asn Asn Val Ser
             20
<210> 193
<211> 22
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:C4BP-BINDING
      PEPTIDE
<400> 193
Ser Gly Ile Ala Gln Phe His Ile Asp Tyr Asn Asn Val Ser Ser Ala
                                                        15
                  5
                                    10
```

Glu Gly Trp His Val Asn 20

```
<210> 194
<211> 34
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:C4BP-BINDING PEPTIDE
```

<400> 194

Leu Val Thr Val Glu Lys Gly Ser Tyr Tyr Pro Gly Ser Gly Ile Ala 1 5 10 15

Gln Phe His Ile Asp Tyr Asn Asn Val Ser Ser Ala Glu Gly Trp His $20 \hspace{1cm} 25 \hspace{1cm} 30$

Val Asn

<210> 196 <211> 17 <212> PRT <213> Artificial Sequence

<400> 196 Ala Glu Pro Met Pro His Ser Leu Asn Phe Ser Gln Tyr Leu Trp Tyr

1 5 10 15

Thr

<210> 197

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:UKR ANTAGONIST PEPTIDE

<400> 197

Ala Glu His Thr Tyr Ser Ser Leu Trp Asp Thr Tyr Ser Prc Leu Ala

1 5 10 15

Phe

<210> 198

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VINCULIN-BINDING PEPTIDE

<400> 198

Ala Glu Leu Asp Leu Trp Met Arg His Tyr Pro Leu Ser Phe Ser Asn
1 5 10 15

Arg

<210> 199

<211> 17

<212> PRT ...

<213> Artificial Sequence

<220> <223> Description of Artificial Sequence: UKR ANTAGONIST PEPTIDE <400> 199 Ala Glu Ser Ser Leu Trp Thr Arg Tyr Ala Trp Pro Ser Met Pro Ser 10 5 Tyr <210> 200 <211> 17 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: UKR ANTAGONIST PEPTIDE <400> 200 Ala Glu Trp His Pro Gly Leu Ser Phe Gly Ser Tyr Leu Trp Ser Lys 10 5 Thr <210> 201 <211> 17 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: UKR ANTAGONIST PEPTIDE <400> 201 Ala Glu Pro Ala Leu Leu Asn Trp Ser Phe Phe Phe Asn Pro Gly Leu 10 5 1

His

```
<210> 202
<211> 17
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:UKR ANTAGONIST
      PEPTIDE
<400> 202
Ala Glu Trp Ser Phe Tyr Asn Leu His Leu Pro Glu Pro Gln Thr Ile
                                                         15
                                     10
                  5
Phe
<210> 203
<211> 17
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence:UKR ANTAGONIST
      PEPTIDE
<400> 203
Ala Glu Pro Leu Asp Leu Trp Ser Leu Tyr Ser Leu Pro Pro Leu Ala
                                     10
                  5
Met
<210> 204
<211> 17
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence:UKR ANTAGONIST
      PEPTIDE
<400> 204
```

Ala Glu Pro Thr Leu Trp Gln Leu Tyr Gln Phe Pro Leu Arg Leu Ser

1 5 10 15

Gly

<210> 205

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<400> 205

Ala Glu Ile Ser Phe Ser Glu Leu Met Trp Leu Arg Ser Thr Pro Ala 1 5 10 15

Phe

<210> 206

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:UKR ANTAGONIST PEPTIDE

<400> 206

Ala Glu Leu Ser Glu Ala Asp Leu Trp Thr Thr Trp Phe Gly Met Gly

1 5 10 15

Ser

<210> 207

<211> 17

<212> PRT-

<213> Artificial Sequence

PCT/US99/25044

WO 00/24782 <220> <223> Description of Artificial Sequence: UKR ANTAGONIST PEPTIDE <400> 207 Ala Glu Ser Ser Leu Trp Arg Ile Phe Ser Pro Ser Ala Leu Met Met 10 5 Ser <210> 208 <211> 17 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: UKR ANTAGONIST PEPTIDE <400> 208 Ala Glu Ser Leu Pro Thr Leu Thr Ser Ile Leu Trp Gly Lys Glu Ser 10 15 5 Va1 <210> 209 <211> 17 <212> PRT <213> Artificial Sequence

<220> <223> Description of Artificial Sequence:UKR ANTAGONIST PEPTIDE

<400> 209 Ala Glu Thr Leu Phe Met Asp Leu Trp His Asp Lys His Ile Leu Leu 10 5 1

Thr

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<210> 210
<211> 17
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: UKR ANTAGONIST
      PEPTIDE
<400> 210
Ala Glu Ile Leu Asn Phe Pro Leu Trp His Glu Pro Leu Trp Ser Thr
                                                          15
                                     10
                  5
  1
Glu
<210> 211
<211> 17
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:UKR ANTAGONIST
      PEPTIDE
<400> 211
Ala Glu Ser Gln Thr Gly Thr Leu Asn Thr Leu Phe Trp Asn Thr Leu
                                                          15
                                     10
 1
Arg
<210> 212
<211> 9
<212> PRT
<213> Artificial Sequence
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <220>
 <223> At position 1, Xaa is V, L, I, E, P, G, Y, M, T,
```

or D

<220>

<223> At position 2, Xaa is Y, W or F

<220>

<223> At position 3, Xaa is E, F, V, W or Y

<220>

<223> At position 5, Xaa is P or azetidine

<220>

<223> At position 7, Xaa is S, A, V or L

<220>

<223> At position 8, Xaa is M, F, V, R, Q, K, T, S, D,
L, I or E

<220>

<223> At position 9, Xaa is E, L, W, V, H, I, G, A, D,
 L, Y, N, Q or P

<400> 212

Xaa Xaa Xaa Gln Xaa Tyr Xaa Xaa Xaa

<210> 213

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<400> 213

Thr Ala Asn Val Ser Ser Phe Glu Trp Thr Pro Tyr Tyr Trp Gln Pro

Tyr Ala Leu Pro Leu

20

<210> 214

<211> 18

```
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 214
Ser Trp Thr Asp Tyr Gly Tyr Trp Gln Pro Tyr Ala Leu Pro Ile Ser
                 5
                                     10
Gly Leu
<210> 215
<211> 21
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 215
Glu Thr Pro Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
                                     10
 1
                 5
Tyr Ala Leu Pro Leu
             20
<210> 216
<211> 21
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
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<400> 216 Glu Asn Thr Tyr Ser Pro Asn Trp Ala Asp Ser Met Tyr Trp Gln Pro

Tyr Ala Leu Pro Leu

1

5

. 10

15

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20

```
<210> 217
<211> 21
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 217
Ser Val Gly Glu Asp His Asn Phe Trp Thr Ser Glu Tyr Trp Gln Pro
                                                         15
                                     10
Tyr Ala Leu Pro Leu
             20
<210> 218
<211> 21
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 218
Asp Gly Tyr Asp Arg Trp Arg Gln Ser Gly Glu Arg Tyr Trp Gln Pro
                                     10
Tyr Ala Leu Pro Leu
             20
<210> 219
<211> 11
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<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

```
<400> 219
Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr
                                    10
<210> 220
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
     PEPTIDE
<400> 220
Phe Glu Trp Thr Pro Gly Tyr Trp Gln His Tyr
 1 5
<210> 221
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 10, Xaa=azetidine
<400> 221
Phe Glu Trp Thr Pro Gly Trp Tyr Gln Xaa Tyr
                  5
<210> 222
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
```

```
<220>
<223> At position 1, optionally acetylated at N-terminus
<220>
<223> At position 10, Xaa=azetidine
<400> 222
Phe Glu Trp Thr Pro Gly Trp Tyr Gln Xaa Tyr
                  5
  1
<210> 223
<211> 12
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 11, Xaa=azetidine
<400> 223
Phe Glu Trp Thr Pro Gly Trp Pro Tyr Gln Xaa Tyr
                  5
<210> 224
 <211> 11
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <223> At position 10, Xaa=azetidine
 Phe Ala Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
                  5
```

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<210> 225
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 10, Xaa=azetidine
<400> 225
Phe Glu Trp Ala Pro Gly Tyr Trp Gln Xaa Tyr
<210> 226
<211> 11
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 10, Xaa=azetidine
<400> 226
Phe Glu Trp Val Pro Gly Tyr Trp Gln Xaa Tyr
                  5
<210> 227
<211> 11
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
 <220>
<223> At position 10, Xaa=azetidine
```

<400> 227

```
Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
                 5
<210> 228
<211> 11
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
     PEPTIDE
<220>
<223> At position 1, optionally acetylated at N-terminus
<223> At position 10, Xaa=azetidine
Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
            5
<210> 229
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<223> At position 6, products="MeGly"
<220>
<223> At position 10, Xaa=azetidine
<400> 229
 Phe Glu Trp Thr Pro Xaa Trp Tyr Gln Xaa Tyr
  1 ... 5
```

```
<210> 230
  <211> 11
  <212> PRT
  <213> Artificial Sequence
  <220>
  <223> Description of Artificial Sequence: IL-1 ANTAGONIST
        PEPTIDE
  <220>
  <223> At position 6, Xaa=MeGly
 <220>
 <223> At position 10, Xaa=azetidine
  <400> 230
Phe Glu Tro Thr Pro Xaa Trp Tyr Gln Xaa Tyr
                    5
                                       10
  <210> 231
  <211> 11
  <212> PRT
  <213> Artificial Sequence
  <220>
  <223> Description of Artificial Sequence: IL-1 ANTAGONIST
        PEPTIDE
  <400> 231
  Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Pro Tyr
                    5
                                       10.
  <210> 232
  <211> 11
  <212> PRT
  <213> Artificial Sequence
  <223> Description of Artificial Sequence: IL-1 ANTAGONIST
        PEPTIDE
  <400> 232
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Phe Glu Trp Thr Pro Gly Trp Trp Gln Pro Tyr

1 5 10

<210> 233

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<400> 233

Phe Glu Trp Thr Pro Asn Tyr Trp Gln Pro Tyr
1 5 10

<210> 234

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<220>

<223> At position 5, Xaa=pipecolic acid

<220>

<223> At position 10, Xaa=azetidine

<400> 234

Phe Glu Trp Thr Xaa Val Tyr Trp Gln Xaa Tyr
1 5 10

<210> 235

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

```
<220>
 <223> At position 5, Xaa=pipecolic acid
 <223> At position 10, Xaa=azetidine
<400> 235
 Phe Glu Trp Thr Xaa Gly Tyr Trp Gln Xaa Tyr
                   5
 <210> 236
 <211> 11
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence:IL-1 ANTAGONIST
       PEPTIDE
 <220>
 <223> At position 6, Xaa=Aib
 <220>
 <223> At position 10, Xaa=azetidine
 <400> 236
 Phe Glu Trp Thr Pro Xaa Tyr Trp Gln Xaa Tyr
                   5
 <210> 237
  <211> 11
 <212> PRT
  <213> Artificial Sequence
  <220>
  <223> Description of Artificial Sequence: IL-1 ANTAGONIST
        PEPTIDE
  <220>
  <223> At position 5, Xaa=MeGly
  <220>
  <223> At position 10, Xaa=azetidine
```

```
<400> 237
Phe Glu Trp Thr Xaa Gly Tyr Trp Gln Xaa Tyr
<210> 238
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 11, amino group added at C-terminus
<400> 238.
Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr
<210> 239
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 11, amino group added at C-terminus
<400> 239
Phe Glu Trp Thr Pro Gly Tyr Trp Gln His Tyr
                   5
<210> 240
```

<211> 11 <212> PRT

<213> Artificial Sequence

```
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
     PEPTIDE
<220>
<223> At position 10, Xaa is an azetidine residue
<220>
<223> At position 11 amino group added at C-terminus
<400> 240
Phe Glu Trp Thr Pro Gly Trp Tyr Gln Xaa Tyr
                  5
<210> 241
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 1, optionally acetylated at
      N-terminus
<220>
<223> At position 10, Xaa is an azetidine residue
<220>
<223> At position 11 amino group added at C-terminus
<400> 241
Phe Glu Trp Thr Pro Gly Trp Tyr Gln Xaa Tyr
                                    10
                  5
<210> 242
<211> 11
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
```

10

PEPTIDE

<220>
<223> At position 8, Xaa is a phyosphotyrosyl residue
<220>
<223> At position 10, Xaa is an azetidine residue
<220>
<223> At position 11, amino group added at C-terminus
<400> 242
Phe Glu Trp Thr Pro Gly Trp Xaa Gln Xaa Tyr

<210> 243 <211> 11 <212> PRT <213> Artificial Sequence

5

<220>

<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

<220>

<223> At position 10, Xaa is an azetidine residue

<220>

<223> At position 11 amino group added at C-terminus

<400> 243

Phe Ala Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 244

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST
 PEPTIDE

<220>

```
<223> At position 10, Xaa is an azetidine residue
<220>
<223> At position 11 amino group added at C-terminus
<400> 244
Phe Glu Trp Ala Pro Gly Tyr Trp Gln Xaa Tyr
                  5
<210> 245
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 10, Xaa is an azetidine residue
<220>
<223> At position 11 amino group added at C-terminus
<400> 245
Phe Glu Trp Val Pro Gly Tyr Trp Gln Xaa Tyr
                                     10
<210> 246
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
 <220>
<223> At position 10, Xaa is an azetidine residue
<220>
<223> At position 11 amino group added at C-terminus
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<400> 246

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 247

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST
 PEPTIDE

<220>

<223> At position 1 acetylated at N-terminus

<220>

<223> At position 10, Xaa is an azetidine residue

<220>

<223> At position 11 amino group added at C-terminus

<400> 247

Xaa Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 248

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST
 PEPTIDE

<220>

<223> At position 6, D amino acid residue

<220>

<223> At position 10, Xaa is an azetidine residue

<220>

<223> At pösition 11 amino group added at C-terminus

<400> 248

Phe Glu Trp Thr Pro Ala Trp Tyr Gln Xaa Tyr 1 5 10

<210> 249

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST
 PEPTIDE

<220>

<223> At position 6, Xaa is a sarcosine residue

<220>

<223> At position 10, Xaa is an azetidine residue

<220>

<223> At position 11 amino group added at C-terminus

<400> 249

Phe Glu Trp Thr Pro Xaa Trp Tyr Gln Xaa Tyr 1 5 10

<210> 250

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

<220>

<223> At position 11 amino group added at C-terminus

<400> 250

Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Pro Tyr

<210> 251

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<211> 11
    <212> PRT
    <213> Artificial Sequence
    <220>
    <223> Description of Artificial Sequence: IL-1 ANTAGONIST
          PEPTIDE
    <220>
    <223> At position 11 amino group added at C-terminus
    <400> 251
    Phe Glu Trp Thr Pro Gly Trp Trp Gln Pro Tyr
           . 5
<210> 252
    <211> 11
    <212> PRT
     <213> Artificial Sequence
     <220>
     <223> Description of Artificial Sequence: IL-1 ANTAGONIST
          PEPTIDE
     <220>
     <223> At position 11 amino group added at C-terminus
     <400> 252
     Phe Glu Trp Thr Pro Asn Tyr Trp Gln Pro Tyr
                                         10
                       5
     <210> 253
     <211> 11
     <212> PRT
     <213> Artificial Sequence
     <220>
     <223> Description of Artificial Sequence: IL-1 ANTAGONIST
           PEPTIDE
     <220>
     <223> At position 6, D amino acid residue
```

<220>

```
<223> At position 10, Xaa is an azetidine residue
<220>
<223> At position 11, amino group added at C-terminus
<400> 253
Phe Glu Trp Thr Pro Val Tyr Trp Gln Xaa Tyr
                  5
<210> 254
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST --
      PEPTIDE
<220>
<223> At position 5, Xaa is a pipecolic acid residue
<220>
<223> At position 10, Xaa is an azetidine residue
<220>
<223> At position 11, amino group added at C-terminus
<400> 254
Phe Glu Trp Thr Xaa Gly Tyr Trp Gln Xaa Tyr
                                      10
  1
                   5
<210> 255
<211> 11
 <212> PRT
 <213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <220>
 <223> At position 6, Xaa=pipecolic acid
```

<220>

```
<223> At position 10, Xaa=azetidine
<400> 255
Phe Glu Trp Thr Pro Xaa Tyr Trp Gln Xaa Tyr
                                     10
                  5
<210> 256
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
     PEPTIDE
<220>
<223> At position 5, Xaa=MeGly
<220>
<223> At position 10, Xaa=azetidine
<400> 256
Phe Glu Trp Thr Xaa Gly Tyr Trp Gln Xaa Tyr
<210> 257
<211> 15
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: INTEGRIN
      BINDING PEPTIDE
<400> 257
Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr Ala Leu Pro Leu
                                     10
                  5
<210> 258
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<211> 11 ···· <212> PRT

<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 1, Xaa is a 1-naphthylalanine residue
<220>
<223> At position 10, Xaa is an azetidine residue
<220>
<223> At position 11, amino group added at C-terminus
<400> 258
Xaa Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr
<210> 259
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 10, Xaa is a azetidine residue
<223> At position 11, amino group added at C-terminus
<400> 259
Tyr Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr
                                      10
                   5
  1
<210> 260
<211> 11
<212> PRT
 <213> Artificial Sequence
 <220>
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<223> Description of Artificial Sequence: IL-1 ANTAGONIST

PEPTIDE

```
<220>
<223> At position 10, Xaa is an azetidine residue

<220>
<223> At position 11, amino group added at C-terminus

<400> 260

Phe Glu Trp Val Pro Gly Tyr Tyr Gln Xaa Tyr

1 5 10
```

<210> 261 <211> 11 <212> PRT <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

<220>

<223> At position 6, D amino acid residue

<220>

<223> At position 10, Xaa is an azetidine residue

<220>

<223> At position 11, amino group added at C-terminus

<400> 261

Phe Glu Trp Thr Pro Ser Tyr Tyr Gln Xaa Tyr 1 5 10

<210> 262

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

<220>

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<223> At position 6, D amino acid residue
<220>
<223> At position 10, Xaa is an azetidine residue
<220>
<223> At position 11, amino group added at C-terminus
<400> 262
Phe Glu Trp Thr Pro Asn Tyr Tyr Gln Xaa Tyr
                                     10
<210> 263
<211> 4
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 263
Thr Lys Pro Arg
  1
<210> 264
<211> 5
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 264
Arg Lys Ser Ser Lys
  1
```

<210> 265 <211> 5 " <212> PRT <213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 265
Arg Lys Gln Asp Lys
 1
<210> 266
<211> 6
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
<400> 266
Asn Arg Lys Gln Asp Lys
 1
<210> 267
<211> 6
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 267
Arg Lys Gln Asp Lys Arg
  1
<210> 268
<211> 9
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
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PEPTIDE

<400> 268
Glu Asn Arg Lys Gln Asp Lys Arg Phe
1 5

<210> 269

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<400> 269

Val Thr Lys Phe Tyr Phe

1

<210> 270

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST
 PEPTIDE

<400> 270

Val Thr Lys Phe Tyr

1

<210> 271

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

<400> 271

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Val Thr Asp Phe Tyr
 1
<210> 272
<211> 17
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
     PEPTIDE
<400> 272
Ser Gly Ser Gly Val Leu Lys Arg Pro Leu Pro Ile Leu Pro Val Thr
                                    10
Arg
<210> 273
<211> 17
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:MCA/MCP
      PROTEASE INHIBITOR PEPTIDE
Arg Trp Leu Ser Ser Arg Pro Leu Pro Pro Leu Pro Leu Pro Pro Arg
                                                        15
                 5
                                    10
Thr
<210> 274
<211> 20
<212> PRT
<213> Artificial Sequence
<220>
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<223> Description of Artificial Sequence:MCA/MCPPROTEASE

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INHIBITOR PEPTIDE

<400> 274

Gly Ser Gly Ser Tyr Asp Thr Leu Ala Leu Pro Ser Leu Pro Leu His 10

Pro Met Ser Ser

<210> 275

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:MCA/MCP PROTEASE INHIBITOR PEPTIDE

<400> 275

Gly Ser Gly Ser Tyr Asp Thr Arg Ala Leu Pro Ser Leu Pro Leu His 10 5

Pro Met Ser Ser

<210> 276

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: MCA/MCP PROTEASE INHIBITOR PEPTIDE

<400> 276

Gly Ser Gly Ser Ser Gly Val Thr Met Tyr Pro Lys Leu Pro Pro His 10

Trp Ser Met Ala

<210> 277

```
<211> 20
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:MCA/MCP
      PROTEASE INHIBITOR PEPTIDE
<400> 277
Gly Ser Gly Ser Ser Gly Val Arg Met Tyr Pro Lys Leu Pro Pro His
                 5 .
                                    10
Trp Ser Met Ala
     . 20
<210> 278
<211> 20
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence:MCA/MCP
      PROTEASE INHIBITOR PEPTIDE
<400> 278
Gly Ser Gly Ser Ser Ser Met Arg Met Val Pro Thr Ile Pro Gly Ser
                                   10
Ala Lys His Gly
·<210> 279
<211> 6
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence:ANTI-HBV
      PEPTIDE
<400> 279
Leu Leu Gly Arg Met Lys
```

```
`<210> 280
<211> 8
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: ANTI-HBV
      PEPTIDE
<400> 280
Ala Leu Leu Gly Arg Met Lys Gly
  1
<210> 281
<211> 6
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: ANTI-HBV
      PEPTIDE
<400> 281
Leu Asp Pro Ala Phe Arg
<210> 282
<211> 7
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: SH3 ANTAGONIST
 <400> 282
 Arg Pro Leu Pro Pro Leu Pro
                   5
  1
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<210> 283 <211> 7

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<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 283
Arg Glu Leu Pro Pro Leu Pro
<210> 284
<211> 7
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: MSH3 ANTAGONIST
<400> 284
Ser Pro Leu Pro Pro Leu Pro
                  5
<210> 285
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 285
Gly Pro Leu Pro Pro Leu Pro
                 5
  1
<210> 286
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
```

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<400> 286
Arg Pro Leu Pro Ile Pro Pro
                  5
<210> 287
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:MAST CELL
      ANTAGONISTS/MAST CELL PROTEASE INHIBITOR
<400> 287
Arg Pro Leu Pro Ile Pro Pro
                  5
  1
<210> 288
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 288
Arg Arg Leu Pro Pro Thr Pro
                 5
  1
<210> 289
<211> 7
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 289
Arg Gln Leu Pro Pro Thr Pro
```

5

```
<210> 290
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 290
Arg Pro Leu Pro Ser Arg Pro
                  5
  1
<210> 291
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 291
Arg Pro Leu Pro Thr Arg Pro
                   5
  1
<210> 292
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
 <400> 292
 Ser Arg Leu Pro Pro Leu Pro
 <210> 293
 <211> 7
 <212> PRT
```

<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 293
Arg Ala Leu Pro Ser Pro Pro
                 5
<210> 294
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 294
Arg Arg Leu Pro Arg Thr Pro
                  5
<210> 295
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 295
Arg Pro Val Pro Pro Ile Thr
  1
<210> 296
<211> 7
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 296---
Ile Leu Ala Pro Pro Val Pro
```

5

1

```
<210> 297
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 297
Arg Pro Leu Pro Met Leu Pro
  1
<210> 298
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 298
Arg Pro Leu Pro Ile Leu Pro
                  5
<210> 299
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 299
Arg Pro Leu Pro Ser Leu Pro
                  5
  1
```

<210> 300 ··· <211> 7 <212> PRT

```
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 300
Arg Pro Leu Pro Ser Leu Pro
                  5
<210> 301
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 301
Arg Pro Leu Pro Met Ile Pro
 1
<210> 302
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 302
Arg Pro Leu Pro Leu Ile Pro
 1
<210> 303
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:SH3 ANTAGONIST
<400> 303
```

```
Arg Pro Leu Pro Pro Thr Pro
1 5
```

. . . .

<210> 304
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:SH3 ANTAGONIST
<400> 304
Arg Ser Leu Pro Pro Leu Pro
1 5

<210> 305
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:SH3 ANTAGONIST
<400> 305
Arg Pro Gln Pro Pro Pro
1 5

<210> 306
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:SH3 ANTAGONIST
<400> 306
Arg Gln Leu Pro Ile Pro Pro
1 5

<210> 307

```
<211> 12
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence:SH3 ANTAGONIST
<400> 307
Xaa Xaa Xaa Arg Pro Leu Pro Pro Leu Pro Xaa Pro
                  5
<210> 308
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 308
Xaa Xaa Xaa Arg Pro Leu Pro Pro Ile Pro Xaa Xaa
                  5
<210> 309
<211> 12
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 309
Xaa Xaa Xaa Arg Pro Leu Pro Pro Leu Pro Xaa Xaa
                  5
<210> 310
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
```

```
<400> 310
Arg Xaa Xaa Arg Pro Leu Pro Pro Leu Pro Xaa Pro
                 5
<210> 311
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 311
Arg Xaa Xaa Arg Pro Leu Pro Pro Leu Pro Pro Pro
                 5----
<210> 312
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 312
Pro Pro Pro Tyr Pro Pro Pro Pro Ile Pro Xaa Xaa
                  5
<210> 313
<211> 12
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 313
Pro Pro Pro Tyr Pro Pro Pro Pro Val Pro Xaa Xaa
```

10

5

```
<210> 314
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<400> 314
Leu Xaa Xaa Arg Pro Leu Pro Xaa Xaa Pro
<210> 315
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<223> At position 1, Xaa is an aliphatic amino acid
      residue
<400> 315
Xaa Xaa Xaa Arg Pro Leu Pro Xaa Leu Pro
                 5
<210> 316
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SH3 ANTAGONIST
<220>
<223> At position 4, Xaa is an aromatic amino acid
      residue
<220>
<223> At position 9, Xaa is an aliphatic amino acid
```

residue

<400> 316
Pro Pro Xaa Xaa Tyr Pro Pro Pro Xaa Pro
1 5 10

<210> 317

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SH3 ANTAGONIST

<220>

<223> At position 1, Xaa is a basic amino acid residue

<220>

<223> At position 4, Xaa is an aliphatic amino acid residue

<400> 317

Xaa Pro Pro Xaa Pro Xaa Lys Pro Xaa Trp Leu 1 5 10

<210> 318

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SH3 ANTAGONIST

<220>

<223> At position 4, Xaa is an aliphatic amino acid residue

<220>

<223> At position 6, Xaa is an aliphatic amino acid residue

<220>

<223> At position 8, Xaa is a basic amino acid residue

<400> 318

Arg Pro Xaa Xaa Pro Xaa Arg Xaa Ser Xaa Pro 1 5 10

<210> 319

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SH3 ANTAGONIST

<400> 319

Pro Pro Val Pro Pro Arg Pro Xaa Xaa Thr Leu

5

<210> 320

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SH3 ANTAGONIST

<220>

<223> At positions 1, 3 and 6, Xaa is an aliphatic amino acid residue

<400> 320

Xaa Pro Xaa Leu Pro Xaa Lys

· 1

<210> 321

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SH3 ANTAGONIST

<220>

<223> At position 1, Xaa is a basic amino acid residue

```
<220>
<223> At position 2, Xaa is an aromatic amino acid
      residue
<400> 321
Xaa Xaa Asp Xaa Pro Leu Pro Xaa Leu Pro
                  5
<210> 322
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: INHIBITOR OF
      PLATELET AGGREGATION
<400> 322
Cys Xaa Xaa Arg Gly Asp Cys
  1
<210> 323
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SRC ANTAGONIST
<400> 323
Arg Pro Leu Pro Pro Leu Pro
                  5
<210> 324
<211> 6
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SRC ANTAGONIST -
```

<400> 324

```
Pro Pro Val Pro Pro Arg
1 5
```

<210> 325

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: ANTI-CANCER PEPTIDE

<400> 325

Xaa Phe Xaa Asp Xaa Trp Xaa Xaa Leu Xaa Xaa

. 5 1

<210> 326

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:p16-MIMETIC PEPTIDE

<400> 326

Lys Ala Cys Arg Arg Leu Phe Gly Pro Val Asp Ser Glu Gln Leu Ser

1 5 10 15

Arg Asp Cys Asp

20

<210> 327

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<400> 327

Arg Glu Arg Trp Asn Phe Asp Phe Val Thr Glu Thr Pro Leu Glu Gly

1 5 10 15

Asp Phe Ala Trp 20

<210> 328

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:p16-MIMETIC PEPTIDE

<400> 328

Lys Arg Arg Gln Thr Ser Met Thr Asp Phe Tyr His Ser Lys Arg Arg 1 5 10 15

Leu Ile Phe Ser 20

<210> 329

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SH3 ANTAGONIST

-400 320

Thr Ser Met Thr Asp Phe Tyr His Ser Lys Arg Arg Leu Ile Phe Ser 1 5 10 15

Lys Arg Lys Pro

20

<210> 330

<211> 5

<212> PRT ...

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:p16-MIMETIC PEPTIDE

<400> 330

Arg Arg Leu Ile Phe

1

<210> 331

<211> 36

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:p16-MIMETIC PEPTIDE

<400> 331

Lys Arg Arg Gln Thr Ser Ala Thr Asp Phe Tyr His Ser Lys Arg Arg 1 5 10 15

Leu Ile Phe Ser Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met 20 25 30

Lys Trp Lys Lys 35

<210> 332

<211> 24

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:p16-MIMETIC
 PEPTIDE

<400> 332

Lys Arg Arg Leu Ile Phe Ser Lys Arg Gln Ile Lys Ile Trp Phe Gln 1 5 10 15

138

Asn Arg Arg Met Lys Trp Lys Lys
20

```
<210> 333
<211> 8
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: POLYGLYCINE
      LINKER
<400> 333
Gly Gly Gly Lys Gly Gly Gly
 1
                 5
<210> 334
<211> 8
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: POLYGLYCINE
      LINKER
<400> 334
Gly Gly Asn Gly Ser Gly Gly
                  5
<210> 335
<211> 8
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: POLYGLYCINE
    LINKER
<400> 335
Gly Gly Gly Cys Gly Gly Gly
                 5
 1
```

<210> 336 <211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:FC PCR PRIMER

<400> 336

Gly Pro Asn Gly Gly

1

5

<210> 337

<211> 42

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO · MIMETIC

<400> 337

Phe Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg. Gln Trp Leu
1 5 10 15

Ala Ala Arg Ala Gly Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro
20 25 30

Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
35 40

<210> 338

<211> 42

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC

<400> 338

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly
1 5 10 15

Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
20 25 30 -----

Ala Ala Arg Ala Gly Gly Gly Gly Phe

35 40

<210> 339

<211> 50

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC

<400> 339

Phe Gly Gly Gly Gly Gly Gly Thr Tyr Ser Cys His Phe Gly Pro

1 5 10 15

Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys Pro Gln 35 40 45

Gly Gly 50

<210> 340

<211> 50

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EPO-MIMETIC

<400> 340

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys

1 5 10 15

Pro Gln Gly Gly Gly Gly Gly Gly Gly Thr Tyr Ser Cys His Phe 20 25 . 30

Gly Pro Leu Thr Trp Val Cys Lys Pro Gln Gly Gly Gly Gly Gly Gly 35

Gly Phe --50

```
<210> 341
<211> 28
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
      PEPTIDES
<400> 341
Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Ile Glu
                  5
Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
             20
<210> 342
<211> 29
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: TPO-MIMETIC
<400> 342
Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Ile
Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
                                25
<210> 343
<211> 30
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: TPO-MIMETIC
<400> 343 ...
Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly
                                    10
                  5
```

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
20 25 30

<210> 344

<211> 31

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC

<400> 344

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly
1 5 10 15

Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala 20 25 30

<210> 345

<211> 32

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC

<400> 345

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly
1 5 10 15

Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala 20 25 30

<210> 346

<211> 33

<212> PRT ...

<213> Artificial Sequence

<220> <223> Description of Artificial Sequence: TPO-MIMETIC <400> 346 Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg 25 Ala <210> 347 <211> 34 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: TPO-MIMETIC <400> 347 Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala 25 Arg Ala <210> 348 <211> 35 <212> PRT <213> Artificial Sequence <223> Description of Artificial Sequence:TPO-MIMETIC <400> 348

Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly

10

5

20 25 30

Ala Arg Ala

<210> 349

<211> 36

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC

<400> 349

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly
1 5 10 15

Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu 20 25 30

Ala Ala Arg Ala

35

<210> 350

<211> 37

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TPO-MIMETIC
 PEPTIDES

<400> 350

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly

1 5 10 15

Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp
20 25 30

Leu Ala Ala Arg Ala

35

<210> 351

<211> 38

<212> PRT

<213> Artificial Sequence

<220>

<400> 351

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly

1 5 10 15

Gly Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln 20 25 30

Trp Leu Ala Ala Arg Ala 35

<210> 352

<211> 42

<212> PRT

<213> Artificial Sequence

<220>

<400> 352

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly
1 5 10 15

Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala 35 40

<210> 353

<211> 32

<212> PRT

<213> Artificial Sequence

<220>

<400> 353

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Pro 1 5 10 15

Asn Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
20 25 30

<210> 354

<211> 36

<212> PRT

<213> Artificial Sequence

<220>

<400> 354

Ile Glu Gly Pro Thr Leu Arg Gln Cys Leu Ala Ala Arg Ala Gly Gly

1 5 10 15

Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Cys Leu 20 25 30

Ala Ala Arg Ala 35

<210> 355

<211> 36

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC PEPTIDES

<400> 355 ...

Ile Glu Gly Pro Thr Leu Arg Gln Cys Leu Ala Ala Arg Ala Gly Gly

1 5 10 15

Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Cys Leu 20 25 30

Ala Ala Arg Ala 35

<210> 356

<211> 36

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC PEPTIDES

<400> 356

Ile Glu Gly Pro Thr Leu Arg Gln Ala Leu Ala Ala Arg Ala Gly Gly
1 5 10 15

Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Ala Leu 20 25 30

Ala Ala Arg Ala 35

<210> 357

<211> 36

<212> PRT

<213> Artificial Sequence

<220>

<400> 357

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly

1 5 10 15

Gly Lys Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu 20 25 30

Ala Ala Arg Ala

35

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<210> 358 <211> 40 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: TPO-MIMETIC PEPTIDES <400> 358 1

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly 10

Gly Lys Asx Arg Ala Cys Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu 25 20

Arg Gln Trp Leu Ala Ala Arg Ala 35

<210> 359 <211> 36

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC PEPTIDES

<400> 359

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly 10

Gly Cys Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu 25

Ala Ala Arg Ala 35

<210> 360 ...

<211> 39

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC PEPTIDES

<400> 360

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly
1 5 10 15

Gly Lys Pro Glu Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg
20 25 30

Gln Trp Leu Ala Ala Arg Ala 35

<210> 361

<211> 39

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TPO-MIMETIC
 PEPTIDES

<400> 361

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly
1 5 10 15

Gly Cys Pro Glu Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg 20 25 30

Gln Trp Leu Ala Ala Arg Ala 35

<210> 362

<211> 36

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TPO-MIMETIC PEPTIDES

<400> 362 Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly . 10 5 Gly Asn Gly Ser Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu . 25 Ala Ala Arg Ala 35 <210> 363 . <211> 36 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: TPO-MIMETIC PEPTIDES <400> 363 Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly 10 Gly Cys Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu 25 Ala Ala Arg Ala 35 <210> 364 <211> 57 <212> DNA <213> Artificial Sequence <220> <223> Description of Artificial Sequence:Fc-TMP PCR PRIMER <400> 364 aaaaaaggat cctcgagatt aagcacgagc agccagccac tgacgcagag tcggacc 57

151

<210> 365 <211> 39

<212>	DNA		
<213>	Artificial Sequence		
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<223>	Description of Artificial Sequence:Fc-TMP PCR		
	PRIMER		
<400>	365		
aaaggt	ggag gtggtggtat cgaaggtccg actctgcgt		39
<210>			
<211>			
<212>			
<213>	Artificial Sequence		
<220>	THE TAXABLE PARTICIPATION AND ADDRESS OF THE PARTICIPATION AND ADR		
<223>	Description of Artificial Sequence: INTEGRIN		
	BINDING PEPTIDE		
-100-			
<400>			42
cagtg	getgg etgetegtge ttaatetega ggateetttt tt		72
<210>	367		
<211>	•		
<212>			
	Artificial Sequence		
-213-	metalional podemos		
<220>			
	Description of Artificial Sequence:Fc-TMP		
<400>	367		
aaaggi	tggag gtggtggtat cgaaggtccg actctgcgtc agtggctggc	tgctcgtgct	60
	togag gatootttt t		81
	•		
<210>	368		
<211>	52		
<212>	DNA		
<213>	Artificial Sequence		
<220>			
<223>	Description of Artificial Sequence: Fc-TMP		
<400>			E 2
ttcga	tacca ccacctccac ctttacccgg agacagggag aggctcttct	gC	52

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<210> 369
<211> 60
<212> DNA
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<223> Description of Artificial Sequence:Fc-TMP-TMP
<400> 369
aaaggtggag gtggtggtat cgaaggtccg actctgcgtc agtggctggc tgctcgtgct 60
<210> 370
<211> 48
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:FC PCR PRIMER
<400> 370
                                                                   48
acctccacca ccagcacgag cagccagcca ctgacgcaga gtcggacc
<210> 371
<211> 66
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:Fc-TMP-TMP
      OLIGONUCLEOTIDE
<400> 371
ggtggtggag gtggcggcgg aggtattgag ggcccaaccc ttcgccaatg gcttgcagca 60
                                                                   66
cgcgca
<210> 372
<211> 76
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:Fc-TMP-TMP
      OLIGONUCLEOTIDE
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<400> 372 aaaaaaagga tootogagat tatgogogtg otgoaagcoa ttggogaagg gttgggooot 60 caatacctcc gccgcc <210> 373 <211> 126 <212> DNA <213> Artificial Sequence <220> <223> Description of Artificial Sequence:Fc-TNF ALPHA PCR PRIMER <220> <221> CDS <222> (1)..(126) <400> 373 aaa ggt gga ggt ggt atc gaa ggt ccg act ctg cgt cag tgg ctg Lys Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu 15 5 1 get get egt get ggt gga ggt gge gga ggt att gag gge eea 96 Ala Ala Arg Ala Gly Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro 20 25 126 acc ctt cgc caa tgg ctt gca gca cgc gca Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala 35 40 <210> 374 <211> 42 <212> PRT <213> Artificial Sequence <223> Description of Artificial Sequence:Fc-TNF ALPHA PCR PRIMER <400> 374 Lys Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu 10 5 Ala Ala Arg Ala Gly Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro 30 20 25 Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala

40

35

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<210> 375
<211> 39
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<221> CDS
<222> (4)..(732)
<400> 375
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ttt ttt cat atg atc gaa ggt ccg act ctg cgt cag tgg
    Phe His Met Ile Glu Gly Pro Thr Leu Arg Gln Trp
                      5
<210> 376
<211> 12
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence:Fc-MMP
      INHIBITOR
<400> 376
Phe His Met Ile Glu Gly Pro Thr Leu Arg Gln Trp
                                     10
<210> 377
<211> 48 -
<212> DNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence:MMP INHIBITOR
      Fc
<220>
<221> CDS
<222> (4)..(753)
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<400> 377 age acg age age cag eea etg acg cag agt egg ace tte gat cat atg Thr Ser Ser Gln Pro Leu Thr Gln Ser Arg Thr Phe Asp His Met 1 5 10 <210> 378 <211> 15 <212> PRT <213> Artificial Sequence <223> Description of Artificial Sequence: MMP INHIBITOR Fc <400> 378 · Thr Ser Ser Gln Pro Leu Thr Gln Ser Arg Thr Phe Asp His Met 10 <210> 379 <211> 45 <212> DNA <213> Artificial Sequence <220> <223> Description of Artificial Sequence:TMP-TMP-Fc OLIGONUCLEOTIDE <400> 379 ctggctgctc gtgctggtgg aggcggtggg gacaaaactc acaca 45 <210> 380 <211> 51 <212> DNA <213> Artificial Sequence <223> Description of Artificial Sequence: INTEGRIN BINDING PEPTIDE <400> 380 ctggctgctc gtgctggcgg tggtggcgga gggggtggca ttgagggccc a <210> 381 ...

<211> 54 <212> DNA

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<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: INTEGRIN
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<400> 381
aagccattgg cgaagggttg ggccctcaat gccacccct ccgccaccac cgcc
<210> 382
<211> 54
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: INTEGRIN
      BINDING PEPTIDE
<400> 382
accettegee aatggettge ageacgegea gggggaggeg gtggggacaa aact
                                                                54
<210> 383
<211> 27
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: INTEGRIN
      BINDING PEPTIDE
<400> 383
                                                                  27
cccaccgcct ccccctgcgc gtgctgc
<210> 384
<211> 189
<212> DNA
<213> Artificial Sequence
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      BINDING PEPTIDE
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<221> CDS
<222> (10)..(189)
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<400> 384

ttttttcat atg atc gaa ggt ccg act ctg cgt cag tgg ctg gct gct cgt 51

Met Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg

1 5 10

gct ggc ggt ggc gga ggg ggt ggc att gag ggc cca acc ctt cgc 99
Ala Gly Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg
15 20 25 30

caa tgg ctg gct gct cgt gct ggt gga ggc ggt ggg gac aaa act ctg 147 Gln Trp Leu Ala Ala Arg Ala Gly Gly Gly Gly Asp Lys Thr Leu 35 40 45

gct gct cgt gct ggt gga ggc ggt ggg gac aaa act cac aca 189
Ala Ala Arg Ala Gly Gly Gly Gly Asp Lys Thr His Thr
50 55 60

<210> 385

<211> 60

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence:INTEGRIN BINDING PEPTIDE

<400> 385

Met Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly

1 5 10 15

Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp
20 25 30

Leu Ala Arg Ala Gly Gly Gly Gly Gly Asp Lys Thr Leu Ala Ala 35 40 45

Arg Ala Gly Gly Gly Gly Asp Lys Thr His Thr
50 55 60

<210> 386

<211> 141

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: INTEGRIN

BINDING PEPTIDE

<400> 386 ctaattccgc tctcacctac caaacaatgc cccctgcaa aaaataaatt catataaaaa 60 acatacagat aaccatctgc ggtgataaat tatctctggc ggtgttgaca taaataccac 120 tggcggtgat actgagcaca t <210> 387 <211> 55 <212> DNA <213> Artificial Sequence <220> <223> Description of Artificial Sequence: INTEGRIN BINDING PEPTIDE <400> 387 cgatttgatt ctagaaggag gaataacata tggttaacgc gttggaattc ggtac 55 <210> 388 <211> 872 <212> DNA <213> Artificial Sequence <220> <223> Description of Artificial Sequence: INTEGRIN BINDING PEPTIDE <400> 388 ttattttcgt gcggccgcac cattatcacc gccagaggta aactagtcaa cacgcacggt 60 gttagatatt tatcccttgc ggtgatagat tgagcacatc gatttgattc tagaaggagg 120 gataatatat gagcacaaaa aagaaaccat taacacaaga gcagcttgag gacgcacgtc 180 gccttaaagc aatttatgaa aaaaagaaaa atgaacttgg cttatcccag gaatctgtcg 240 cagacaagat ggggatgggg cagtcaggcg ttggtgcttt atttaatggc atcaatgcat 300 taaatgctta taacgccgca ttgcttacaa aaattctcaa agttagcgtt gaagaattta 360 gcccttcaat cgccagagaa tctacgagat gtatgaagcg gttagtatgc agccgtcact 420 tagaagtgag tatgagtacc ctgttttttc tcatgttcag gcagggatgt tctcacctaa 480 gettagaace tttaccaaag gtgatgegga gagatgggta agcacaacca aaaaagccag 540 tgattctgca ttctggcttg aggttgaagg taattccatg accgcaccaa caggctccaa 600 gccaagcttt cctgacggaa tgttaattct cgttgaccct gagcaggctg ttgagccagg 660 tgatttctgc atagccagac ttgggggtga tgagtttacc ttcaagaaac tgatcaggga 720 tageggteag gtgtttttae aaccactaaa eccacagtae ecaatgatee catgeaatga 780 gagttgttcc gttgtgggga aagttatcgc tagtcagtgg cctgaagaga cgtttggctg 840

atagactagt ggatccacta gtgtttctgc cc

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<210> 389
<211> 1197
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: INTEGRIN
     BINDING PEPTIDE
<400> 389
qqcqqaaacc qacqtccatc qaatqqtqca aaacctttcg cggtatgqca tgataqcqcc 60
cggaagagag tcaattcagg gtggtgaatg tgaaaccagt aacgttatac gatgtcgcag 120.
agtatgccgg tgtctcttat cagaccgttt cccgcgtggt gaaccaggcc agccacgttt 180
ctgcgaaaac gcgggaaaaa gtcgaagcgg cgatggcgga gctgaattac attcccaacc 240
gcgtggcaca acaactggcg ggcaaacagt cgctcctgat tggcgttgcc acctccagtc 300
tggccctgca cgcgccgtcg caaattgtcg cggcgattaa atctcgcgcc gatcaactgg 360
gtgccagcgt ggtggtgtcg atggtagaac gaagcggcgt cgaagcctgt aaagcggcgg 420
tgcacaatct tctcgcgcaa cgcgtcagtg ggctgatcat taactatccg ctggatgacc 480
aggatgccat tgctgtggaa gctgcctgca ctaatgttcc ggcgttattt cttgatgtct 540
ctgaccagac acccatcaac agtattattt tctcccatga agacggtacg cgactgggcg 600
tggagcatct ggtcgcattg ggtcaccagc aaatcgcgct gttagcgggc ccattaagtt 660
ctgtctcggc gcgtctgcgt ctggctggct ggcataaata tctcactcgc aatcaaattc 720
agccgatagc ggaacgggaa ggcgactgga gtgccatgtc cggttttcaa caaaccatgc 780
aaatgctgaa tgagggcatc gttcccactg cgatgctggt tgccaacgat cagatggcgc 840
tgggcgcaat gcgcgccatt accgagtccg ggctgcgcgt tggtgcggat atctcggtag 900
tgggatacga cgataccgaa gacagctcat gttatatccc gccgttaacc accatcaaac 960
aggattttcg cctgctgggg caaaccagcg tggaccgctt gctgcaactc tctcagggcc 1020
cgcccaatac gcaaaccgcc tctccccgcg cgttggccga ttcattaatg cagctggcac 1140
gacaggtttc ccgactggaa agcggacagt aaggtaccat aggatccagg cacagga
<210> 390
<211> 61
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:Fc-EMP
      OLIGONUCLEOTIDE
<400> 390
tatgaaaggt ggaggtggtg gtggaggtac ttactcttgc cacttcggcc cgctgacttg 60
                                                                61
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<210> 391 <211> 72

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<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:Fc-EMP
      OLIGONUCLEOTIDE
<400> 391
cggtttgcaa acccaagtca gcgggccgaa gtggcaagag taagtacctc caccaccacc 60
tccacctttc at
<210> 392
<211> 57
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:Fc-EMP
      OLIGONUCLEOTIDE
 <400> 392
gtttgcaaac cgcagggtgg cggcggcggc ggcggtggta cctattcctg tcatttt
                                                                   57
 <210> 393
 <211> 60
 <212> DNA
 <213> Artificial Sequence
<220>
 <223> Description of Artificial Sequence:Fc-EMP
       OLIGONUCLEOTIDE
 <400> 393
 ccaggtcage gggccaaaat gacaggaata ggtaccaccg ccgccgccgc cgccaccctg 60
 <210> 394
 <211> 118
 <212> DNA
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<223> Description of Artificial Sequence:Fc-EMP PCR TEMPLATE

<213> Artificial Sequence

<220>

<221> CDS

<222> (2)..(118)

<400> 394

t atg aaa ggt gga ggt ggt ggt gga ggt act tac tct tgc cac ttc ggc 49 Met Lys Gly Gly Gly Gly Gly Gly Thr Tyr Ser Cys His Phe Gly 1 5 10

ccg ctg act tgg gtt tgc aaa ccg cag ggt ggc ggc ggc ggc ggc ggt 97
Pro Leu Thr Trp Val Cys Lys Pro Gln Gly Gly Gly Gly Gly Gly 20
25
30

ggt acc tat tcc tgt cat ttt Gly Thr Tyr Ser Cys His Phe 35 118

<210> 395

<211> 39

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence:Fc-EMP PCR
 TEMPLATE

<400> 395

Met Lys Gly Gly Gly Gly Gly Gly Thr Tyr Ser Cys His Phe Gly
1 5 10 15

Gly Thr Tyr Ser Cys His Phe 35

<210> 396

<211> 61

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Fc-EMP PCR PRIMER

<400> 396

gcagaagagc ctctccctgt ctccgggtaa aggtggaggt ggtggtggag gtacttactc 60

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<210> 397
<211> 40
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:Fc-EMP PCR
      PRIMER
<400> 397
                                                                   40
ctaattggat ccacgagatt aaccaccctg cggtttgcaa
<210> 398
<211> 22
<212> DNA ···
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:Fc PRIMER
<400> 398
                                                                   22
aacataagta cctgtaggat cg
<210> 399
<211> 61
<212> DNA
<213> Artificial Sequence
<223> Description of Artificial Sequence:Fc PRIMER
<400> 399
agagtaagta cctccaccac cacctccacc tttacccgga gacagggaga ggctcttctg 60
 <210> 400
 <211> 61
 <212> DNA
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: EMP-Fc
       OLIGONUCLEOTIDE
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<400> 400
ggcccgctga cctgggtatg taagccacaa gggggtgggg gaggcggggg gtaatctcga 60
<210> 401
<211> 50
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EMP-Fc
    OLIGONUCLEOTIDE
<400> 401
gatcctcgag attacccccc gcctccccca cccccttgtg gcttacatac
                                                                 50
<210> 402
<211> 118
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EMP-Fc PCR
      TEMPLATE
<220>
<221> CDS
<222> (1)..(108)
<400> 402
gtt tgc aaa ccg cag ggt ggc ggc ggc ggc ggt ggt acc tat tcc
Val Cys Lys Pro Gln Gly Gly Gly Gly Gly Gly Gly Thr Tyr Ser
tgt cat ttt ggc ccg ctg acc tgg gta tgt aag cca caa ggg ggt ggg
Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys Pro Gln Gly Gly
             20
                                                    30
                                                                 118
gga ggc ggg ggg taatctcgag
Gly Gly Gly
         35
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<210> 403 <211> 36

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<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: EMP-Fc PCR
<400> 403
Val Cys Lys Pro Gln Gly Gly Gly Gly Gly Gly Gly Thr Tyr Ser
                  5
                                    10
Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys Pro Gln Gly Gly
                                 25
             20
Gly Gly Gly Gly
         35
<210> 404
<211> 39
<212> DNA
<213> Artificial Sequence
<223> Description of Artificial Sequence: EMP-Fc PCR
      PRIMER
<400> 404
                                                                 39
ttatttcata tgaaaggtgg taactattcc tgtcatttt
<210> 405
<211> 43
<212> DNA
<213> Artificial Sequence
<223> Description of Artificial Sequence: EMP-Fc PCR
      PRIMER
<400> 405
                                                                  43
tggacatgtg tgagttttgt ccccccgcc tcccccaccc cct
<210> 406
<211> 43
<212> DNA
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<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence:Fc PRIMER
<400> 406
agggggtggg ggaggcgggg gggacaaaac tcacacatgt cca
                                                                  43
<210> 407
<211> 20
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:Fc PRIMER
<400> 407
                                                                  20
gttattgctc agcggtggca
<210> 408
<211> 60
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EMP-EMP-Fc
      OLIGONUCLEOTIDE
<400> 408
ttttttatcg atttgattct agatttgagt tttaactttt agaaggagga ataaaatatg 60
<210> 409
<211> 41
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EMP-EMP-Fc
      OLIGONUCLEOTIDE
<400> 409
                                                                   41
taaaagttaa aactcaaatc tagaatcaaa tcgataaaaa a
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<210> 410 ··· <211> 51

<212> DNA

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<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EMP-EMP-Fc
      OLIGONUCLEOTIDE
<400> 410
ggaggtactt actcttgcca cttcggcccg ctgacttggg tttgcaaacc g
                                                                  51
<210> 411
<211> 55
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EMP-EMP-Fc
      OLIGONUCLEOTIDE
<400> 411
agtcagcggg ccgaagtggc aagagtaagt acctcccata ttttattcct ccttc
                                                                  55
<210> 412
<211> 60
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EMP-EMP-Fc
      OLIGONUCLEOTIDE
<400> 412
cagggtggcg gcggcggcgg cggtggtacc tattcctgtc attttggccc gctgacctgg 60
<210> 413
<211> 60
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EMP-EMP-Fc
      OLIGONUCLEOTIDE
aaaatgacag gaataggtac caccgccgcc gccgccgcca ccctgcggtt tgcaaaccca 60
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<210> 414
 <211> 57
 <212> DNA
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: EMP-EMP-Fc
       OLIGONUCLEOTIDE
 <400> 414
                                                                 57
 gtatgtaagc cacaaggggg tggggggagc gggggggaca aaactcacac atgtcca
 <210> 415
 <211> 60
 <212> DNA
<213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: EMP-EMP-Fc
       OLIGONUCLEOTIDE
 <400> 415
 agttttgtcc cccccgcctc ccccaccccc ttgtggctta catacccagg tcagcgggcc 60
 <210> 416
 <211> 228
  <212> DNA
 <213> Artificial Sequence
 <223> Description of Artificial Sequence: EMP-EMP-Fc PCR
       TEMPLATE
 <220>
 <221> CDS
  <222> (58)..(228)
  <400> 416
 ttttttatcg atttgattct agatttgagt tttaactttt agaaggagga ataaaat
 atg gga ggt act tac tct tgc cac ttc ggc ccg ctg act tgg gtt tgc
 Met Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys
                                      10
                    5
  aaa ccg cag ggt ggc ggc ggc ggc ggt ggt acc tat tcc tgt cat
                                                                    153
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Lys Pro Gln Gly Gly Gly Gly Gly Gly Gly Thr Tyr Ser Cys His 20 25 30

ttt ggc ccg ctg acc tgg gta tgt aag cca caa ggg ggt ggg gga ggc 201
Phe Gly Pro Leu Thr Trp Val Cys Lys Pro Gln Gly Gly Gly Gly
35 40 45

ggg ggg gac aaa act cac aca tgt cca 228
Gly Gly Asp Lys Thr His Thr Cys Pro
50 55

<210> 417

<211> 57

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence:EMP-EMP-Fc PCR
 TEMPLATE

<400> 417

Met Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys
1 5 10 15

Lys Pro Gln Gly Gly Gly Gly Gly Gly Gly Thr Tyr Ser Cys His 20 25 30

Phe Gly Pro Leu Thr Trp Val Cys Lys Pro Gln Gly Gly Gly Gly Gly 35 40 45

Gly Gly Asp Lys Thr His Thr Cys Pro 50 55

<210> 418

<211> 40

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Fc-EMP-EMP PCR
PRIMER

<400> 418

ctaattggat cctcgagatt aacccccttg tggcttacat

40

<210> 419

<211> 72

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EPO-MIMETIC PEPTIDE

<400> 419

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa 65 70

<210> 420

<211> 62

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EPO-MIMETIC PEPTIDE

<400> 420

Xaa Tyr Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Aaa Gly Pro 1 5 10 15

Xaa Xaa Xaa Xaa Xaa Xaa Thr Trp Xaa Xaa Xaa Xaa Xaa Xaa Cys . 20 25 30

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<210> 421
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EPO-MIMETIC
      PEPTIDE
<220>
<223> At position 2, Xaa is R, H, L or W
<220>
<223> At position 3, Xaa is M, F or I
<223> At position 6, Xaa is any of the 20 genetically
      encoded amino acid residues or a D-stereoisomer
      thereof
<220>
<223> At position 9, Xaa is D, E, I, L or V
<400> 421
Cys Xaa Xaa Gly Pro Xaa Thr Trp Xaa Cys
<210> 422
<211> 19
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EPO-MIMETIC
       PEPTIDE
<400> 422
Gly Gly Thr Tyr Ser Cys His Gly Pro Leu Thr Trp Val Cys Lys Pro
                                                          15
                                      10
                   5
 1
 Gln Gly Gly
```

```
<210> 423
<211> 19
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EPO-MIMETIC
      PEPTIDE
<400> 423
Val Gly Asn Tyr Met Ala His Met Gly Pro Ile Thr Trp Val Cys Arg
                  5
                                     10
Pro Gly Gly
<210> 424
<211> 18
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EPO-MIMETIC
      PEPTIDE
<400> 424
Gly Gly Pro His His Val Tyr Ala Cys Arg Met Gly Pro Leu Thr Trp
                                      10
                  5
Ile Cys
<210> 425
<211> 18
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: EPO-MIMETIC
      PEPTIDE
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<400> 425
Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys

1 5 10 15

Pro Gln

<210> 426

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<400> 426

Gly Gly Leu Tyr Ala Cys His Met Gly Pro Met Thr Trp Val Cys Gln
1 5 10 15

Pro Leu Arg Gly

20

<210> 427

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<400> 427

Thr Ile Ala Gln Tyr Ile Cys Tyr Met Gly Pro Glu Thr Trp Glu Cys
1 5 10 15

Arg Pro Ser Pro Lys Ala

20

<210> 428

<211> 13

<212> PRT...

<213> Artificial Sequence

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<220>
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<223> Description of Artificial Sequence: EPO-MIMETIC PEPTIDE

<400> 428

Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10

<210> 429

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EPO MIMETIC PEPTIDE

<400> 429

Tyr Cys His Phe Gly Pro Leu Thr Trp Val Cys 1 5 10

<210> 430

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:UKR ANTAGONIST
 PEPTIDE

<400> 430

Ala Glu Pro Val Tyr Gln Tyr Glu Leu Asp Ser Tyr Leu Arg Ser Tyr 1 5 10 15

Tyr

<210> 431

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:UKR ANTAGONIST PEPTIDE

<400> 431

Ala Glu Leu Asp Leu Ser Thr Phe Tyr Asp Ile Gln Tyr Leu Leu Arg

1 5 10 15

Thr

<210> 432

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:UKR ANTAGONIST PEPTIDE

<400> 432

Ala Glu Phe Phe Lys Leu Gly Pro Asn Gly Tyr Val Tyr Leu His Ser 1 5 10 15

Ala

<210> 433

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:UKR ANTAGONIST
 PEPTIDE

<400> 433

Phe Lys Leu Xaa Xaa Xaa Gly Tyr Val Tyr Leu
1 5 10

<210> 434

<211> 17

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:UKR ANTAGONIST
PEPTIDE

<400> 435
Tyr His Xaa Leu Xaa Xaa Gly Tyr Met Tyr Thr
1 5 10

<210> 437 <211> 4

<210> 435 <211> 11

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<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:MCA/MCP
      INHIBITOR
<400> 437
Arg Asn Arg Gln
 1
<210> 438
<211> 5
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:MCA/MCP
      INHIBITOR
<400> 438
Arg Asn Arg Gln Lys
 1
<210> 439
<211> 5
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:MCA/MCP
      INHIBITOR
<400> 439
Asn Arg Gln Lys Thr
  1 5
<210> 440
<211> 4
<212> PRT
```

<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence:MCA/MCP
      INHIBITOR
<400> 440
Arg Gln Lys Thr
 1
<210> 441
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial
      Sequence: INTEGRIN-BINDING PEPTIDE
<400> 441
Arg Xaa Glu Thr Xaa Trp Xaa
  1
<210> 442
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial
      Sequence: INTEGRIN-BINDING PEPTIDE
<400> 442
Arg Xaa Glu Thr Xaa Trp Xaa
            5 ·
<210> 443
<211> 5
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial
      Sequence: INTEGRIN-BINDING PEPTIDE
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<400> 443 Arg Gly Asp Gly Xaa 1 5

<210> 444

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial
 Sequence:INTEGRIN-BINDING PEPTIDE

<400> 444

Cys Arg Gly Asp Gly Xaa Cys

<210> 445

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial
 Sequence:INTEGRIN-BINDING PEPTIDE

<400> 445

Cys Xaa Xaa Arg Leu Asp Xaa Xaa Cys

<210> 446

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial
 Sequence:INTEGRIN-BINDING PEPTIDE

<400> 446 ...

Cys Ala Arg Arg Leu Asp Ala Pro Cys

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5 1

<210> 447

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: INTEGRIN-BINDING PEPTIDE

<400> 447

Cys Pro Ser Arg Leu Asp Ser Pro Cys 5

<210> 448

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: INTEGRIN-BINDING PEPTIDE

<400> 448

Xaa Xaa Xaa Arg Gly Asp Xaa Xaa Xaa 5

<210> 449

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: INTEGRIN-BINDING PEPTIDE

<400> 449

Cys Xaa Cys Arg Gly Asp Cys Xaa Cys

5 ...

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<210> 450
<211> 9
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial
      Sequence: INTEGRIN-BINDING PEPTIDE
<400> 450
Cys Asp Cys Arg Gly Asp Cys Phe Cys
<210> 451
<211> 9
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial
      Sequence: INTEGRIN-BINDING PEPTIDE
<400> 451
Cys Asp Cys Arg Gly Asp Cys Leu Cys
                  5
<210> 452
<211> 9
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial
      Sequence: INTEGRIN-BINDING PEPTIDE
<400> 452
Cys Leu Cys Arg Gly Asp Cys Ile Cys
                   5
  1
```

<210> 453 <211> 8

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<212> PRT
<213> Artificial Sequence
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<220>

<223> Description of Artificial
 Sequence:INTEGRIN-BINDING PEPTIDE

<400> 453 Xaa Xaa Asp Asp Xaa Xaa Xaa Xaa 1 5

<210> 454 <211> 10 <212> PRT <213> Artificial Sequence

<220>
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 Sequence:INTEGRIN-BINDING PEPTIDE

<210> 455 <211> 8 <212> PRT <213> Artificial Sequence <220>

<223> Description of Artificial
 Sequence:INTEGRIN-BINDING PEPTIDE

<400> 455 Cys Trp Asp Asp Gly Trp Leu Cys 1 5

<210> 456 <211> 9 <212> PRT ... <213> Artificial Sequence

<220>

<223> Description of Artificial
 Sequence:INTEGRIN-BINDING PEPTIDE

<400> 456

Cys Trp Asp Asp Leu Trp Trp Leu Cys
1 5

<210> 457

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial
 Sequence:INTEGRIN-BINDING PEPTIDE

<400> 457

Cys Trp Asp Asp Gly Leu Met Cys
1 5

<210> 458

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial
 Sequence:INTEGRIN-BINDING PEPTIDE

<400> 458

Cys Trp Asp Asp Gly Trp Met Cys

1

5

<210> 459

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial
 Sequence:INTEGRIN-BINDING PEPTIDE

<400> 459
Cys Ser Trp Asp Asp Gly Trp Leu Cys
1 5 .

<210> 460

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial
 Sequence:INTEGRIN-BINDING PEPTIDE

<400> 460

Cys Pro Asp Asp Leu Trp Trp Leu Cys

1 5

<210> 461

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<400> 461

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Aaa 35

<210> 462

<211> 16

<212> PRT---

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SELECTIN ANTAGONIST PEPTIDE

<400> 462

Cys Gln Asn Arg Tyr Thr Asp Leu Val Ala Ile Gln Asn Lys Asn Glu
1 5 10 15

<210> 463

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial
 Sequence:SELECTIN-ANTAGONIST PEPTIDE

<400> 463

Ala Glu Asn Trp Ala Asp Asn Glu Pro Asn Asn Lys Arg Asn Asn Glu

1 5 10 15

Asp

<210> 464

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SELECTIN ANTAGONIST PEPTIDE

<400> 464

Arg Lys Asn Asn Lys Thr Trp Thr Trp Val Gly Thr Lys Lys Ala Leu 1 5 10 15

Thr Asn Glu

<210> 465

<211> 13

```
<212> PRT
```

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SELECTIN ANTAGONIST PEPTIDE

<400> 465

Lys Lys Ala Leu Thr Asn Glu Ala Glu Asn Trp Ala Asp
1 5 10

<210> 466

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SELECTIN ANTAGONIST PEPTIDE

<400> 466

Cys Gln Xaa Arg Tyr Thr Asp Leu Val Ala Ile Gln Asn Lys Xaa Glu 1 5 10 15

<210> 467

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SELECTIN ANTAGONIST PEPTIDE

<400> 467

Arg Lys Xaa Asn Xaa Xaa Trp Thr Trp Val Gly Thr Xaa Lys Xaa Leu 1 5 10 15

Thr Glu Glu

<210> 468

<211> 17

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<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: SELECTIN
      ANTAGONIST PEPTIDE
<400> 468
Ala Glu Asn Trp Ala Asp Gly Glu Pro Asn Asn Lys Xaa Asn Xaa Glu
                                     10
qsA
<210> 469
<211> 16
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: SELECTIN
      ANTAGONIST PEPTIDE
<400> 469
Cys Xaa Xaa Xaa Tyr Thr Xaa Leu Val Ala Ile Gln Asn Lys Xaa Glu
                                    10
                 5
<210> 470
<211> 19
<212> PRT
<213> Artificial Sequence
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<220> <223> Description of Artificial Sequence: SELECTIN ANTAGONIST PEPTIDE

<400> 470 Arg Lys Xaa Xaa Xaa Trp Xaa Trp Val Gly Thr Xaa Lys Xaa Leu 10 1

Thr Xaa Glu

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<210> 471
<211> 16
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SELECTIN
      ANTAGONIST PEPTIDE
<400> 471
Ala Xaa Asn Trp Xaa Xaa Xaa Glu Pro Asn Asn Xaa Xaa Xaa Glu Asp
<210> 472
<211> 13
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SELECTIN
      ANTAGONIST PEPTIDE
<400> 472
Xaa Lys Xaa Lys Thr Xaa Glu Ala Xaa Asn Trp Xaa Xaa
<210> 473
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SOMATOSTATIN/
      CORTISTATIN-MIMETIC PEPTIDE
<220>
<223> At position 1, Xaa is asp-arg-met-pro-cys,
      arg-met-pro-cys, met-pro-cys, pro-cys, or cys
<223> At position 2, Xaa is arg or lys
```

<220>

```
<223> At position 10, Xaa is ser or thr
 <220>
 <223> At position 12, xaa is cys-lys or cys
 <400> 473
 Xaa Xaa Asn Phe Phe Trp Lys Thr Phe Xaa Ser Xaa
                  5
 <210> 474
 <211> 18
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: SOMATOSTATIN/
       CORTISTATIN-MIMETIC PEPTIDE
 <400> 474
 Asp Arg Met Pro Cys Arg Asn Phe Phe Phe Trp Lys Thr Phe Ser Ser
                   5
                                      10
 Cys Lys
 <210> 475
<211> 15
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: SOMATOSTATIN/
       CORTISTATIN-MIMETIC PEPTIDE
 <400> 475
 Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys
                                      .10
 <210> 476
  <211> 13 ...
  <212> PRT
  <213> Artificial Sequence
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<220> <223> Description of Artificial Sequence: SOMATOSTATIN/ CORTISTATIN-MIMETIC PEPTIDE <400> 476 Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys 5 <210> 477 <211> 16 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: SOMATOSTATIN/ CORTISTATIN-MIMETIC PEPTIDE <400> 477 Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys 10 5 <210> 478 <211> 14 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence:SOMATOSTATIN/ CORTISTATIN MIMETIC PEPTIDE <400> 478 Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys 10 5 <210> 479 <211> 12 <212> PRT <213> Artificial Sequence <220>

<223> Description of Artificial Sequence: SOMATOSTATIN/

CORTISTATIN MIMETIC PEPTIDE

<400> 479
Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10

<210> 480

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:SOMATOSTATIN/ CORTISTATIN MIMETIC PEPTIDE

<400> 480

Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys

1 5 10 15

<210> 481

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SOMATOSTATIN/ CORTISTATIN MIMETIC PEPTIDE

<400> 481

Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys
1 5 10 15

<210> 482

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<400> 482

```
Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys
1 5 10
```

<210> 483 <211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:SOMATOSTATIN/ CORTISTATIN MIMETIC PEPTIDE

<400> 483

Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys

1 5 10 15

<210> 484

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Fc-TMP

<400> 484

Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10

<210> 485

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 485

Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10

```
<210> 486
<211> 17
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SOMATOSTATIN/
     CORTISTATIN MIMETIC PEPTIDE
<400> 486
Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
                                   10
                 5
Lys
<210> 487
<211> 15
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: SOMATOSTATIN/
      CORTISTATIN MIMETIC PEPTIDE
<400> 487
Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys
                                    10
                 5
<210> 488
<211> 13
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SOMATOSTATIN/
      CORTISTATIN MIMETIC PEPTIDE
<400> 488
Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys
 1 ... 5
                                   10
```

```
<210> 489
<211> 16
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SOMATOSTATIN/
      CORTISTATIN MIMETIC PEPTIDE
<400> 489
Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
                                                         15
                                     10
<210> 490
<211> 14
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SOMATOSTATIN/
      CORTISTATIN MIMETIC PEPTIDE
<400> 490
Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
                  5
                                     10
<210> 491
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SOMATOSTATIN/
      CORTISTATIN MIMETIC PEPTIDE
<400> 491
Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
                                     10
         _ 5
```

<210> 492 <211> 17

<212> PRT

<213> Artificial Sequence

<220>

<400> 492

Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys

1 10 15

Lys

<210> 493

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<400> 493

Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys
1 5 10 15

<210> 494

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<400> 494

Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys
1 5 10

<210> 495

<211> 16

```
<212> PRT .
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SOMATOSTATIN/
     CORTISTATIN MIMETIC PEPTIDE
<400> 495
Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
                                    10
                  5
<210> 496
<211> 14
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SOMATOSTATIN/
    CORTISTATIN MIMETIC PEPTIDE
<400> 496
Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
<210> 497
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: SOMATOSTATIN/
      CORTISTATIN MIMETIC PEPTIDE
Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
                 5
                                    10
```

<210> 498 <211> 25 <212> PRT

<213> Artificial Sequence

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<220>

<223> Description of Artificial Sequence:CAP37 MIMETIC/LPS BINDING PEPTIDE

<400> 498

Asn Gln Gly Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe 10

Val Met Thr Ala Ala Ser Cys Phe Gln 20 25

<210> 499

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: CAP37 MIMETIC/LPS BINDING PEPTIDE

<400> 499

Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr 15 10

Ala Ala Ser Cys

20

<210> 500

<211> 27

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: CAP37 MIMETIC/LPS BINDING PEPTIDE

<400> 500

Gly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly 10 5 1

Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val ... 20

```
<210> 501
<211> 18
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: VEGF-ANTAGONIST
      PEPTIDE
<400> 501
Gly Glu Arg Trp Cys Phe Asp Gly Pro Arg Ala Trp Val Cys Gly Trp
                                     10
Glu Ile
<210> 502
<211> 18
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: VEGF ANTAGONIST
      PEPTIDE
<400> 502
Glu Glu Leu Trp Cys Phe Asp Gly Pro Arg Ala Trp Val Cys Gly Tyr
                                     10
Val Lys
<210> 503
<211> 33
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: ANTIPATHOGENIC
      PEPTIDE
<400> 503
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Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu Phe Lys

1 5 10 15

Thr Leu Leu Ser Ala Val Gly Ser Ala Leu Ser Ser Ser Gly Gly Gln 20 25 30

Gln

<210> 504

<211> 33

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: ANTIPATHOGENIC PEPTIDE

<220>

<223> At positions 7, 18 and 19, D amino acid residue

<400> 504

Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu Phe Lys
1 5 10 15

Thr Leu Leu Ser Ala Val Gly Ser Ala Leu Ser Ser Ser Gly Gly Gln 20 25 30

Glu

<210> 505

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: ANTIPATHOGENIC PEPTIDE

<220>

<223> At positions 18 and 19, D amino acid residues

<400> 505

Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu Phe Lys

1 5 10 15

Thr Leu Leu Ser Ala Val 20

<210> 506

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<220>

<223> At positions 7, 18 and 19, D amino acid residues

<400> 506

Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu Phe Lys
1 5 10 15

Thr Leu Leu Ser Ala Val

20

<210> 507

<211> 23

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<220>

<223> At positions 8, 19 and 20, D amino acid residues

<400> 507

Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu Phe 1 5 10 15

Lys Thr Leu Leu Ser Ala Val

20

```
<210> 508
<211> 24
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
     PEPTIDE
<220>
<223> At positions 9, 20 and 21, D amino acid residues
<400> 508
Lys Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu
                5
                                   10
Phe Lys Thr Leu Leu Ser Ala Val
             20
<210> 509
<211> 24
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<220>
<223> At positions 9, 20 and 21, D amino acid residues
<400> 509
Lys Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu
                                                        15
                                    10
 1
                  5
Phe Lys Thr Leu Leu Ser Ala Val
             20
```

<210> 510 <211> 11 <212> PRT <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<220>

<223> At position 7, D amino acid residue

<400> 510

Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser

<210> 511

<211> 26

<212> PRT

<213> Artificial Sequence

<220>

<400> 511

Gly Ile Gly Ala Val Leu Lys Val Leu Thr Thr Gly Leu Pro Ala Leu

1 5 10 15

Ile Ser Trp Ile Lys Arg Lys Arg Gln Gln 20 25

<210> 512

<211> 26

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<220>

<223> At positions 5, 8, 17 and 23, D amino acid residues

<400> 512

Gly Ile Gly Ala Val Leu Lys Val Leu Thr Thr Gly Leu Pro Ala Leu

1 5 10 15

Ile Ser Trp Ile Lys Arg Lys Arg Gln Gln
20 25

<210> 513

<211> 26

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<220>

<223> At positions 5, 8, 17 and 23, D amino acid residues

<400> 513

Gly Ile Gly Ala Val Leu Lys Val Leu Thr Thr Gly Leu Pro Ala Leu

1 5 10 15

Ile Ser Trp Ile Lys Arg Lys Arg Gln Gln 20 25

<210> 514

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<220>

<223> At positions 5, 8, 17 and 21, D amino acid residues

<400> 514

Gly Ile Gly Ala Val Leu Lys Val Leu Thr Thr Gly Leu Pro Ala Leu

1 5 10 15

Ile Ser Trp Ile Lys Arg

... 20

```
<210> 515
<211> 19
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<220>
<223> At positions 2, 5, 14 and 18, D amino acid
      residues
<400> 515
Ala Val Leu Lys Val Leu Thr Thr Gly Leu Pro Ala Leu Ile Ser Trp
                5
                                    10
Ile Lys Arg
<210> 516
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<223> At positions 3, 4, 8 and 10, D amino acid residues
<400> 516
Lys Leu Leu Leu Leu Lys Leu Leu Leu Lys
                                    10
                 5
<210> 517
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
```

<223> Description of Artificial Sequence:VIP MIMETIC

PEPTIDE

<220>
<223> At positions 3, 4, 8 and 10, D amino acid residues
<400> 517
Lys Leu Leu Leu Lys Leu Leu Lys Leu Leu Lys
1 5 10

<210> 519 <211> 12 <212> PRT <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 519
Lys Lys Leu Leu Lys Leu Lys Leu Lys Leu Lys Lys
1 5 10

<210> 520 <211> 12 <212> PRT <213> Artificial Sequence

```
<220>
   <223> Description of Artificial Sequence: VIP MIMETIC
         PEPTIDE
   <400> 520
   Lys Leu Leu Lys Leu Leu Leu Lys Leu Lys
                    5
    <210> 521
    <211> 12
    <212> PRT
    <213> Artificial Sequence
    <220>
<223> Description of Artificial Sequence:VIP MIMETIC
         PEPTIDE
    <400> 521
    Lys Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys
                                       10
     1
    <210> 522
    <211> 6
    <212> PRT
    <213> Artificial Sequence
    <220>
    <223> Description of Artificial Sequence: VIP MIMETIC
          PEPTIDE
    <400> 522
    Lys Leu Leu Leu Lys
     1
    <210> 523
     <211> 8
     <212> PRT
     <213> Artificial Sequence
     <220>
    <223> Description of Artificial Sequence:VIP MIMETIC
```

PEPTIDE

<400> 523 Lys Leu Leu Leu Lys Leu Leu Lys 1 5

<210> 524 <211> 12

<212> PRT <213> Artificial Sequence

<220>

Lys Leu Leu Lys Leu Lys Leu Lys Leu Lys 1 5 10

<210> 525

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 525

Lys Leu Leu Lys Leu Lys Leu Lys Leu Lys 1 5 10

<210> 526

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 526

```
Lys Leu Leu Lys Leu Lys Leu Lys Leu Lys
1 5 10
```

<210> 527

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 527

Lys Ala Ala Lys Ala Ala Lys Ala Ala Lys

1 5 10 .

<210> 528

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 528

Lys Val Val Val Lys Val Val Lys Val Val Lys

1 5 10

<210> 529

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 529 ...

Lys Val Val Val Lys Val Lys Val Lys Val Val Lys

1 5 10

```
<210> 530
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 530
Lys Val Val Lys Val Lys Val Lys Val Lys
 1 5
<210> 531
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 531
Lys Val Val Lys Val Lys Val Lys Val Val Lys
                                    10
 <210> 532
 <211> 6
 <212> PRT
<213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence:VIP MIMETIC
       PEPTIDE
 <400> 532
 Lys Leu Ile Leu Lys Leu
```

<210> 533

```
<211> 6
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 533
Lys Val Leu His Leu Leu
<210> 534
<211> 6
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 534
Leu Lys Leu Arg Leu Leu
 1
<210> 535
<211> 6
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
 <400> 535
 Lys Pro Leu His Leu Leu
  1
```

```
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 536
Lys Leu Ile Leu Lys Leu Val Arg
                 5
<210> 537
<211> 8
<212> PRT
<213> Artificial Sequence
<220>
 <223> Description of Artificial Sequence: VIP MIMETIC
       PEPTIDE
 <400> 537
 Lys Val Phe His Leu Leu His Leu
                  5
 <210> 538
 <211> 8
 <212> PRT
  <213> Artificial Sequence
  <220>
  <223> Description of Artificial Sequence:VIP MIMETIC
        PEPTIDE
  <400> 538
  His Lys Phe Arg Ile Leu Lys Leu
                    5
  <210> 539
  <211> 8
  <212> PRT
  <213> Artificial Sequence
  <220>
  <223> Description of Artificial Sequence:VIP MIMETIC
```

PEPTIDE

<400> 539 Lys Pro Phe His Ile Leu His Leu 1 5

<210> 540

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 540 - ----

Lys Ile Ile Ile Lys Ile Lys Ile Lys Ile Ile Lys
1 5 10

<210> 541

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 541

Lys Ile Ile Ile Lys Ile Lys Ile Lys Ile Ile Lys

1 5 10

<210> 542

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 542

Lys Ile Ile Ile Lys Ile Lys Ile Lys Ile Ile Lys
1 5 10

<210> 543

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 543

Lys Ile Pro Ile Lys Ile Lys Ile Lys Ile Pro Lys
1 5 10

<210> 544

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 544

Lys Ile Pro Ile Lys Ile Lys Ile Lys Ile Val Lys
1 5 10

<210> 545

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 545

Arg Ile Ile Ile Arg Ile Arg Ile Arg Ile Ile Arg
1 5 10

```
<210> 546
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
     PEPTIDE
<400> 546
Arg Ile Ile Ile Arg Ile Arg Ile Arg Ile Ile Arg
 1 . 5
<210> 547
<211> 12
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 547
Arg Ile Ile Ile Arg Ile Arg Ile Arg Ile Ile Arg
                5
<210> 548
<211> 12
<212> PRT
<213> Artificial Sequence
 <223> Description of Artificial Sequence:VIP MIMETIC
     PEPTIDE
 <400> 548
 Arg Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg
```

<210> 549

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 549

Arg Ile Ile Val Arg Ile Arg Leu Arg Ile Ile Arg
1 5 10

<210> 550

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 550

Arg Ile Gly Ile Arg Leu Arg Val Arg Ile Ile Arg
1 5 10

<210> 551

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 551

Lys Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg

1 5 10

<210> 552

<211> 12 ...

<212> PRT

<213> Artificial Sequence

```
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 552
Arg Ile Ala Val Lys Trp Arg Leu Arg Phe Ile Lys
                  5
                                     10
<210> 553
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 553
Lys Ile Gly Trp Lys Leu Arg Val Arg Ile Ile Arg
                                     10
                  5
<210> 554
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 554
Lys Lys Ile Gly Trp Leu Ile Ile Arg Val Arg Arg
                5
 1
<210> 555
<211> 14
```

<223> Description of Artificial Sequence: VIP MIMETIC

<212> PRT

<220>

<213> Artificial Sequence

PEPTIDE

<400> 555
Arg Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg Ile Arg
1 5 10

<210> 556

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 556

Arg Ile Ile Val Arg Ile Arg Leu Arg Ile Ile Arg Val Arg
1 5 10

<210> 557

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<400> 557

Arg Ile Gly Ile Arg Leu Arg Val Arg Ile Ile Arg Arg Val
1 5 10

<210> 558

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 558

Lys Ile Val Ile Arg Ile Arg Ala Arg Leu Ile Arg Ile Arg Ile Arg

```
10
<210> 559
<211> 16
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
     PEPTIDE
<400> 559
Arg Ile Ile Val Lys Ile Arg Leu Arg Ile Ile Lys Lys Ile Arg Leu
                5
1
<210> 560
<211> 16
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 560
Lys Ile Gly Ile Lys Ala Arg Val Arg Ile Ile Arg Val Lys Ile Ile
                  5
                                    10
<210> 561
<211> 16.
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 561
Arg Ile Ilë Val His Ile Arg Leu Arg Ile Ile His His Ile Arg Leu
```

10

1 5

```
<210> 562
<211> 16
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence:VIP MIMETIC
       PEPTIDE
 <400> 562
 His Ile Gly Ile Lys Ala His Val Arg Ile Ile Arg Val His Ile Ile
                 5
                                     10
 <210> 563
 <211> 16
 <212> PRT
 <213> Artificial Sequence
 <223> Description of Artificial Sequence:VIP MIMETIC
       PEPTIDE
 <400> 563
 Arg Ile Tyr Val Lys Ile His Leu Arg Tyr Ile Lys Lys Ile Arg Leu
  1
                                     10
 <210> 564
 <211> 16
 <212> PRT
<213> Artificial Sequence
 <223> Description of Artificial Sequence:VIP MIMETIC
       PEPTIDE
 <400> 564
Lys Ile Gly His Lys Ala Arg Val His Ile Ile Arg Tyr Lys Ile Ile
                                     10
                                                        15
                  5
```

<210> 565

```
<211> 16
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence:VIP MIMETIC
     PEPTIDE
<400> 565
Arg Ile Tyr Val Lys Pro His Pro Arg Tyr Ile Lys Lys Ile Arg Leu
                5
                                  10
<210> 566
<211> 16
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence:VIP MIMETIC
    PEPTIDE
<400> 566
Lys Pro Gly His Lys Ala Arg Pro His Ile Ile Arg Tyr Lys Ile Ile
                5
                                   10
<210> 567
<211> 19
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 567
Lys Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg Ile Arg
                                   10
Lys Ile Val
```

<210> 568

```
<211> 19
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 568
Arg Ile Ile Val Lys Ile Arg Leu Arg Ile Ile Lys Lys Ile Arg Leu
                  5
                                     10
Ile Lys Lys
<210> 569
 <211> 19
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: VIP MIMETIC
       PEPTIDE
 <400> 569
 Lys Ile Gly Trp Lys Leu Arg Val Arg Ile Ile Arg Val Lys Ile Gly
               . 5
                                                         15
   1
Arg Leu Arg
 <210> 570
 <211> 25
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: VIP MIMETIC
       PEPTIDE
 <400> 570
 Lys Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg Ile Arg
```

5

1

10

Lys Ile Val Lys Val Lys Arg Ile Arg 20 25

<210> 571

<211> 26

<212> PRT

<213> Artificial Sequence

<220>

<400> 571

Arg Phe Ala Val Lys Ile Arg Leu Arg Ile Ile Lys Lys Ile Arg Leu

1 5 10 15

Ile Lys Lys Ile Arg Lys Arg Val Ile Lys 20 25

<210> 572

<211> 30

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 572

Lys Ala Gly Trp Lys Leu Arg Val Arg Ile Ile Arg Val Lys Ile Gly

1 5 10 15

Arg Leu Arg Lys Ile Gly Trp Lys Lys Arg Val Arg Ile Lys 20 25 30

<210> 573

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC

PEPTIDE

<400> 573

Arg Ile Tyr Val Lys Pro His Pro Arg Tyr Ile Lys Lys Ile Arg Leu

1 5 10 15

<210> 574

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 574

Lys Pro Gly His Lys Ala Arg Pro His Ile Ile Arg Tyr Lys Ile Ile
1 5 10 15

<210> 575

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 575

Lys Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg Ile Arg Ile Arg Ile Arg I

Lys Ile Val

<210> 576

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC

PEPTIDE

<400> 576

Arg Ile Ile Val Lys Ile Arg Leu Arg Ile Ile Lys Lys Ile Arg Leu

1 5 10 15

Ile Lys Lys

<210> 577

<211> 16

<212> PRT .

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: VIP MIMETIC PEPTIDE

<400> 577

Arg Ile Tyr Val Ser Lys Ile Ser Ile Tyr Ile Lys Lys Ile Arg Leu
1 5 10 15

<210> 578

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 578

Lys Ile Val Ile Phe Thr Arg Ile Arg Leu Thr Ser Ile Arg Ile Arg 1 5 10 15

Ser Ile Val

<210> 579

<211> 16 ...

<212> PRT

<213> Artificial Sequence

<220> <223> Description of Artificial Sequence: VIP MIMETIC PEPTIDE <400> 579 Lys Pro Ile His Lys Ala Arg Pro Thr Ile Ile Arg Tyr Lys Met Ile 10 <210> 580 <211> 26 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: VIP MIMETIC PEPTIDE <220> <223> At position 1, disulfide bond to position 26 <220> <223> At position 26, disulfide bond to position 1 <400> 580 Xaa Cys Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro 1 5 10 Leu Phe Lys Thr Leu Leu Ser Ala Val Cys 20 25 <210> 581 <211> 26 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE <400> 581 Cys Lys Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser_Pro

5

1

10

Leu Phe Lys Thr Leu Leu Ser Ala Val Cys
20 25

<210> 582

<211> 27

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 582

Cys Lys Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser 1 5 10 15

Pro Leu Phe Lys Thr Leu Leu Ser Ala Val Cys
20 25

<210> 583

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<220>

<223> At position 1, disulfide bond to position 17

<220>

<223> At position 17, disulfide bond to position 1

<400> 583

Xaa Cys Arg Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg Ile Arg 1 1 5 10 15

Cys

<210> 584

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<220>

<223> At position 1, disulfide bond to position 19

<220>

<223> At position 19, disulfide bond to position 1

<400> 584

Xaa Cys Lys Pro Gly His Lys Ala Arg Pro His Ile Ile Arg Tyr Lys

1 5 10 15

Ile Ile Cys

<210> 585

<211> 29

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC
 PEPTIDE

<220>

<223> At position 1, disulfide bond to position 29

<220>

<223> At position 29, disulfide bond to position 1

<400> 585

Xaa Cys Arg Phe Ala Val Lys Ile Arg Leu Arg Ile Ile Lys Lys Ile 1 5 10 15

Arg Leu Ile Lys Lys Ile Arg Lys Arg Val Ile Lys Cys 20 25

<210> 586

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<211> 13
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 586
Lys Leu Leu Lys Leu Leu Lys Leu Leu Lys Cys
<210> 587
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 587
Lys Leu Leu Lys Leu Leu Lys Leu Lys
                 5
<210> 588
<211> 13
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 588
Lys Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys Cys
```

<210> 589 <211> 12 ... <212> PRT <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 589

Lys Leu Leu Lys Leu Leu Leu Lys Leu Leu Lys

1 5 10

<210> 590

<211> 28

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 590

His Ser Asp Ala Val Phe Tyr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Leu Asn 20 25

<210> 591

<211> 31

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 591

Asn Leu Glu His Ser Asp Ala Val Phe Tyr Asp Asn Tyr Thr Arg Leu

1 5 .10 15

Arg Lys Gln Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Leu Asn 20 25 30

<210> 592

```
<211> 4
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<220>
<223> At position 1, Xaa is absent or is ala, val,
      ala-val, val-ala, L-lys, D-lys, ala-lys, val-lys,
      ala-val-lys, val-ala-lys, or an ornithinyl residue
<220>
<223> At position 2, Xaa is L-lys, D-lys or an
      ornithinyl residue
<220>
<223> At position 3, Xaa is L-tyr, D-tyr, phe, trp or a
      p-aminophenylalanyl residue
<220>
<223> At position 4, Xaa is a hydrophobic aliphatic
      amino acid residue (X5), X5-leu, X5-norleucyl,
      X5-D-ala, X5-asn-ser, X5-asn-ser-ile,
      X5-asn-ser-tyr, X5-asn-ser-ile-leu,
      X5-asn-ser-tyr-leu,
<220>
<223> or X5-asn-ser-tyr-leu-asn
<400> 592
Xaa Xaa Xaa Xaa
  1
<210> 593
<211> 5
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
```

<223> At position 1, Xaa is either absent, a hydrophobic

PEPTIDE

<220>

aliphatic residue (X5), X5-asn, tyr-X5, lys-X5, lyx-S5-asn, lys-tyr-X5, lys-tyr-X5-as, lys-lys-tyr-X5-asn, val-lys-lys-tyr-X5,

<220>

<223> val-ala-lys-lys-tyr-X5-asn, or
 ala-val-lys-lys-tyr-X5-asn

<220>

<223> At position 3, Xaa is ile or tyr

<400> 593

Xaa Ser Xaa Leu Asn

<210> 594

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<220>

<223> At positions 1 and 6, Xaa are cross-linked amino
 acid residues in which the sidechain linker group
 is (CH2)m-Z-(CH2)n wherein Z is -CONH-, -NHCO-,
 -S-S-, -S(CH2)tCO-NH or -NH-CO(CH2)tS-; m is 1 or
2

<220>

<223> when Z is -NH-CO- or -NH-CO(CH2)tS-; n is 1 or 2
 when Z is -NH-CO-, -S-S- or -NH-CO(CH2)tS, or n is
2, 3 or 4 when Z is -CONH- or -S(CH2)tCO-NH-

<220>

<223> At position 5, Xaa is a hydrophobic aliphatic amino acid residue

<220>

<223> At position 7, Kaa is a covalent bond or Asn, Ser, Ile, Tyr, Leu, Asn-Ser, Asn-Ser-Ile, Asn-Ser-Tyr, Asn-Ser-Ile-Leu, Asn-Ser-Tyr-Leu, Asn-Ser-Ile-Leu-Asn or Asn-Ser-Tyr-Leu-Asn

```
<400> 594
Xaa Lys Lys Tyr Xaa Xaa Xaa
 1
                  5
<210> 595
<211> 4
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
     PEPTIDE
<400> 595
Lys Lys Tyr Leu
1
<210> 596
<211> 5
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
     PEPTIDE
<400> 596
Asn Ser Ile Leu Asn
                  5
 1
<210> 597
<211> 4
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
```

<400> 597 Lys Lys Tyr Leu

1

```
<210> 598
<211> 4
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<220>
<223> At position 4, D amino acid residue
<400> 598
Lys Lys Tyr Ala
<210> 599
<211> 6
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 599
Ala Val Lys Lys Tyr Leu
 1
<210> 600
<211> 5
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 600 ...
```

Asn Ser Ile Leu Asn

1 5

```
<210> 601
<211> 4
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
<400> 601
Lys Lys Tyr Val
 1
<210> 602
<211> 4
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
     PEPTIDE
<223> At position 3, Xaa is a lauric acid residue
<400> 602
Ser Ile Xaa Asn
 1
<210> 603
<211> 5
<212> PRT
<213> Artificial Sequence
<220>
```

<220>
<223> At position 5, Xaa is a norleucyl residue

PEPTIDE

<223> Description of Artificial Sequence:VIP MIMETIC

```
<400> 603
Lys Lys Tyr Leu Xaa
 1
<210> 604
<211> 5
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 604
Asn Ser Tyr Leu Asn
  1
<210> 605
<211> 5
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 605
Asn Ser Ile Tyr Asn
  1
<210> 606
<211> 11
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 606
```

Lys Lys Tyr Leu Pro Pro Asn Ser Ile Leu Asn

1 5 10

<210> 608
<211> 5
<212> PRT
<213> Artificial Sequence
<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<223> At position 1, Xaa is a caproic acid residue
<400> 608
Xaa Lys Lys Tyr Leu

<210> 609 <211> 4 <212> PRT <213> Artificial Sequence

<220>

<220>
<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

```
<220>
<223> At position 4, Xaa is a norleucyl residue
<400> 609
Lys Lys Tyr Xaa
 1
<210> 610
<211> 5
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
    PEPTIDE
<400> 610
Val Lys Lys Tyr Leu
<210> 611
<211> 6
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 611
Leu Asn Ser Ile Leu Asn
  1
                 5 ·
<210> 612
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
```

```
<400> 612
Tyr Leu Asn Ser Ile Leu Asn
                  5
<210> 613
<211> 5
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 613
Lys Lys Tyr Leu Asn
 <210> 614
 <211> 6
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: VIP MIMETIC
 <400> 614
 Lys Lys Tyr Leu Asn Ser
                  5
 <210> 615
 <211> 7
 <212> PRT
 <213> Artificial Sequence
 <220>
<223> Description of Artificial Sequence: VIP MIMETIC
       PEPTIDE
 <400> 615 ...
```

Lys Lys Tyr Leu Asn Ser Ile

1 5

```
<210> 616
<211> 8
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
     PEPTIDE
<400> 616
Lys Lys Tyr Leu Asn Ser Ile Leu
 1
<210> 617
<211> 4
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
```

<400> 617 Lys Lys Tyr Leu 1

```
<210> 619
<211> 6
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 619
Ala Val Lys Lys Tyr Leu
  1
                  5
<210> 620
<211> 5
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 620
Asn Ser Ile Leu Asn
<210> 621
<211> 4
<212> PRT
<213> Artificial Sequence
<220>
 <223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 621
 Lys Lys Tyr Val
  1
```

·

240

<210> 622 <211> 4

```
<212> PRT
<213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence:VIP MIMETIC
       PEPTIDE
 <220>
 <223> At position 3, Xaa is a lauric acid residue
 <400> 622
 Ser Ile Xaa Asn
  1
 <210> 623
 <211> 5
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence:VIP MIMETIC
       PEPTIDE
 <400> 623
 Asn Ser Tyr Leu Asn
 <210> 624
 <211> 5
  <212> PRT
 <213> Artificial Sequence
 <220>
  <223> Description of Artificial Sequence:VIP MIMETIC
        PEPTIDE
  <400> 624
  Asn Ser Ile Tyr Asn
    1
```

<210> 625 <211> 5

```
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<220>
<223> At position 5, Xaa is a norleucyl residue
<400> 625
Lys Lys Tyr Leu Xaa
 1
<210> 626
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 626
Lys Lys Tyr Leu Pro Pro Asn Ser Ile Leu Asn
                  5
<210> 627
<211> 4
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 627
Lys Lys Tyr Leu
 1
```

<210> 628 <211> 5

```
<212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence:VIP MIMETIC
       PEPTIDE
 <400> 628
 Lys Lys Tyr Asp Ala
 <210> 629
  <211> 6
  <212> PRT
  <213> Artificial Sequence
 <220>
  <223> Description of Artificial Sequence:VIP MIMETIC
       PEPTIDE
  <400> 629
  Ala Val Lys Lys Tyr Leu
   1
                  5
  <210> 630
  <211> 5
 <212> PRT
  <213> Artificial Sequence
  <220>
  <223> Description of Artificial Sequence:VIP MIMETIC
        PEPTIDE
  <400> 630
  Asn Ser Ile Leu Asn
<210> 631
  <211> 4
  <212> PRT
```

<213> Artificial Sequence

```
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
     PEPTIDE
<400> 631
Lys Lys Tyr Val
 1
<210> 632
<211> 4
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
    PEPTIDE
<220>
<223> At position 3, Xaa is a lauric acid residue.
<400> 632
Ser Ile Xaa Asn
 1
<210> 633
<211> 6
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
     PEPTIDE
<400> 633
Leu Ala Lys Lys Tyr Leu
                5
 1
<210> 634
<211> 7
<212> PRT--
<213> Artificial Sequence
```

```
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
<400> 634
Cys Ala Pro Lys Lys Tyr Leu
<210> 635
<211> 4
<212> PRT
 <213> Artificial Sequence
<220>
 <223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<220>
 <223> At position 4, Xaa is a norleucyl residue
<400> 635
 Lys Lys Tyr Xaa
  1
 <210> 636
 <211> 5
<212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: VIP MIMETIC
       PEPTIDE
 <400> 636
 Val Lys Lys Tyr Leu
 <210> 637
 <211> 6
 <212> PRT ...
 <213> Artificial Sequence
```

```
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 637
Leu Asn Ser Ile Leu Asn
<210> 638
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 638
Tyr Leu Asn Ser Ile Leu Asn
 1
                   5
 <210> 639
 <211> 5
 <212> PRT
 <213> Artificial Sequence
 <223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
 <220>
 <223> At position 5, Xaa is a norleucyl residue
 <400> 639
 Lys Lys Tyr Leu Xaa
  1
 <210> 640
 <211> 5
 <212> PRT ...
 <213> Artificial Sequence
```

```
<220>
 <223> Description of Artificial Sequence: VIP MIMETIC
       PEPTIDE
 <400> 640
 Lys Lys Tyr Leu Asn
 <210> 641
 <211> 6
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence:VIP MIMETIC
 <400> 641
 Lys Lys Tyr Leu Asn Ser
 <210> 642
 <211> 7
 <212> PRT
 <213> Artificial Sequence
<220>
 <223> Description of Artificial Sequence:VIP MIMETIC
       PEPTIDE
 <400> 642
 Lys Lys Tyr Leu Asn Ser Ile
 <210> 643
 <211> 8
 <212> PRT
 <213> Artificial Sequence
 <220>
  <223> Description of Artificial Sequence: VIP MIMETIC
```

PEPTIDE

```
<400> 643
 Lys Lys Tyr Leu Asn Ser Ile Leu
                  5
 <210> 644
 <211> 6
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
 <400> 644
 Lys Lys Lys Tyr Leu Asp
<210> 645
 <211> 7
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence:VIP MIMETIC
       PEPTIDE
 <220>
 <223> At positions 1, 6 disulfide cross-linked
 <400> 645
 Xaa Cys Lys Lys Tyr Leu Cys
                 5
 <210> 646
 <211> 6
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence:VIP MIMETIC
       PEPTIDE
```

```
<220>
<223> At positions 1, 6 cross-linked by S-CH2-CO
<400> 646
Cys Lys Lys Tyr Leu Lys
<210> 647
<211> 4
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<220>
<223> At position 4, D amino acid residue
<400> 647
Lys Lys Tyr Ala
<210> 648
<211> 8
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 648
Trp Trp Thr Asp Thr Gly Leu Trp
  1
<210> 649
<211> 8
<212> PRT
<213> Artificial Sequence
```

```
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
     PEPTIDE
<400> 649
Trp Trp Thr Asp Asp Gly Leu Trp
<210> 650
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 650
Trp Trp Asp Thr Arg Gly Leu Trp Val Trp Thr Ile
                  5
<210> 651
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 651
Phe Trp Gly Asn Asp Gly Ile Trp Leu Glu Ser Gly
                  5
<210> 652
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:VIP MIMETIC
```

PEPTIDE

```
<400> 652
Asp Trp Asp Gln Phe Gly Leu Trp Arg Gly Ala Ala
1 5 10
```

<210> 653

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC
 PEPTIDE

<400> 653

Arg Trp Asp Asp Asn Gly Leu Trp Val Val Val Leu
1 5 10

<210> 654

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 654

Ser Gly Met Trp Ser His Tyr Gly Ile Trp Met Gly
1 5 10

<210> 655

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 655

Gly Gly Arg Trp Asp Gln Ala Gly Leu Trp Val Ala

5 10 1

<210> 656

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: VIP MIMETIC PEPTIDE

<400> 656

Lys Leu Trp Ser Glu Gln Gly Ile Trp Met Gly Glu 10 5

<210> 657

<211> 10

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence: VIP MIMETIC PEPTIDE

<400> 657

Cys Trp Ser Met His Gly Leu Trp Leu Cys 5

<210> 658

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: VIP MIMETIC PEPTIDE

<400> 658

Gly Cys Trp Asp Asn Thr Gly Ile Trp Val Pro Cys *** 5

```
<210> 659
<211> 10
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 659
Asp Trp Asp Thr Arg Gly Leu Trp Val Tyr
                 5
<210> 660
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 660
Ser Leu Trp Asp Glu Asn Gly Ala Trp Ile
                  5
<210> 661
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
 <223> Description of Artificial Sequence: VIP MIMETIC
       PEPTIDE
<400> 661
 Lys Trp Asp Asp Arg Gly Leu Trp Met His
  1
                   5
```

<210> 662 <211> 10

```
<212> PRT
```

<213> Artificial Sequence

<223> Description of Artificial Sequence: VIP MIMETIC PEPTIDE

<400> 662

Gln Ala Trp Asn Glu Arg Gly Leu Trp Thr 5

<210> 663

<211> 10

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 663

Gln Trp Asp Thr Arg Gly Leu Trp Val Ala 5

<210> 664

<211> 9

. <212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

<400> 664

Trp Asn Val His Gly Ile Trp Gln Glu 5

1

<210> 665

<211> 10

<212> PRT

<213> Artificial Sequence

```
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 665
Ser Trp Asp Thr Arg Gly Leu Trp Val Glu
                 5
<210> 666
<211> 10
```

<212> PRT <213> Artificial Sequence <220>

<223> Description of Artificial Sequence: VIP MIMETIC

<400> 666 Asp Trp Asp Thr Arg Gly Leu Trp Val Ala

<210> 667 <211> 10 <212> PRT <213> Artificial Sequence

<220> <223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

Ser Trp Gly Arg Asp Gly Leu Trp Ile Glu

<210> 668 <211> 10 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence:VIP MIMETIC PEPTIDE

```
<400> 668
Glu Trp Thr Asp Asn Gly Leu Trp Ala Leu
                                      10
                  5
<210> 669
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VIP MIMETIC
      PEPTIDE
<400> 669
Ser Trp Asp Glu Lys Gly Leu Trp Ser Ala
                  5
<210> 670
<211> 10
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence:VIP MIMETIC
      PEPTIDE
<400> 670
Ser Trp Asp Ser Ser Gly Leu Trp Met Asp
<210> 671
 <211> 11
<212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <400> 671
```

Ser His Leu Tyr Trp Gln Pro Tyr Ser Val Gln

1 5 10

<210> 672

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 672

Thr Leu Val Tyr Trp Gln Pro Tyr Ser Leu Gln Thr

5

<210> 673

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 673

Arg Gly Asp Tyr Trp Gln Pro Tyr Ser Val Gln Ser

1 5 10

<210> 674

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 674

Val His Val Tyr Trp Gln Pro Tyr Ser Val Gln Thr

```
<210> 675
 <211> 12
 <212> PRT
 <213> Artificial Sequence
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <400> 675
 Arg Leu Val Tyr Trp Gln Pro Tyr Ser Val Gln Thr
                                      10
                 5
 <210> 676
<211> 12
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <400> 676
 Ser Arg Val Trp Phe Gln Pro Tyr Ser Leu Gln Ser
                  -5
 <210> 677
 <211> 12
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <400> 677
 Asn Met Val Tyr Trp Gln Pro Tyr Ser Ile Gln Thr
                   5
```

<210> 678 <211> 12

```
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 678
Ser Val Val Phe Trp Gln Pro Tyr Ser Val Gln Thr
                                    10
                 5
<210> 679
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 679
Thr Phe Val Tyr Trp Gln Pro Tyr Ala Leu Pro Leu
            5
<210> 680
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 680
Thr Leu Val Tyr Trp Gln Pro Tyr Ser Ile Gln Arg
         5
                                    10
```

<210> 681 <211> 12 <212> PRT-<213> Artificial Sequence <220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

<400> 681

Arg Leu Val Tyr Trp Gln Pro Tyr Ser Val Gln Arg
1 5 10

<210> 682

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 682

Ser Pro Val Phe Trp Gln Pro Tyr Ser Ile Gln Ile
1 5 10

<210> 683

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST
 PEPTIDE

<400> 683

Trp Ile Glu Trp Trp Gln Pro Tyr Ser Val Gln Ser

1 5 10

<210> 684

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

```
<400> 684
Ser Leu Ile Tyr Trp Gln Pro Tyr Ser Leu Gln Met
                  5
  1
<210> 685
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 685
Thr Arg Leu Tyr Trp Gln Pro Tyr Ser Val Gln Arg
                  5
<210> 686
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 686
Arg Cys Asp Tyr Trp Gln Pro Tyr Ser Val Gln Thr
                  5
<210> 687
<211> 12
 <212> PRT
 <213> Artificial Sequence
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
```

<400> 687 Met Arg Val Phe Trp Gln Pro Tyr Ser Val Gln Asn

PEPTIDE

1 5 10

```
<210> 688
<211> 12
<212> PRT
```

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST
 PEPTIDE

<400> 688

Lys Ile Val Tyr Trp Gln Pro Tyr Ser Val Gln Thr
1 5 10

<210> 689

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST
 PEPTIDE

<400> 689

Arg His Leu Tyr Trp Gln Pro Tyr Ser Val Gln Arg
1 5 10

<210> 690

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 690

Ala Leu Val Trp Trp Gln Pro Tyr Ser Glu Gln Ile
1 5 10

```
<210> 691
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 691
Ser Arg Val Trp Phe Gln Pro Tyr Ser Leu Gln Ser
                                     10
                 5
<210> 692
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
     PEPTIDE
<400> 692
Trp Glu Gln Pro Tyr Ala Leu Pro Leu Glu
                                     10
                  5
<210> 693
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 693
Gln Leu Val Trp Trp Gln Pro Tyr Ser Val Gln Arg
                                     10
                   5
  1
```

<210> 694 <211> 12

```
<212> PRT
```

<213> Artificial Sequence

<220>

<400> 694

Asp Leu Arg Tyr Trp Gln Pro Tyr Ser Val Gln Val
1 5 10

<210> 695

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 695

Glu Leu Val Trp Trp Gln Pro Tyr Ser Leu Gln Leu

1 5 10

<210> 696

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST
 PEPTIDE

<400> 696

Asp Leu Val Trp Trp Gln Pro Tyr Ser Val Gln Trp
1 5 10

<210> 697

<211> 12

<212> PRT--

<213> Artificial Sequence

```
WO 00/24782
<220>
<223> Description of Artificial Sequence:IL-1 ANTAGONIST
     PEPTIDE
<400> 697
Asn Gly Asn Tyr Trp Gln Pro Tyr Ser Phe Gln Val
                  5
<210> 698
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
    PEPTIDE
<400> 698
Glu Leu Val Tyr Trp Gln Pro Tyr Ser Ile Gln Arg
                 5
<210> 699
<211> 12
<212> PRT
<213> Artificial Sequence
```

<220> <223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE <400> 699 Glu Leu Met Tyr Trp Gln Pro Tyr Ser Val Gln Glu 5

```
<210> 700
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
```

```
<400> 700
Asn Leu Leu Tyr Trp Gln Pro Tyr Ser Met Gln Asp
                  5
<210> 701
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
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Gly Tyr Glu Trp Tyr Gln Pro Tyr Ser Val Gln Arg
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Leu Ser Glu Gln Tyr Gln Pro Tyr Ser Val Gln Arg

<400> 703

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<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

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Gly Gly Gly Trp Trp Gln Pro Tyr Ser Val Gln Arg
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Val Gly Arg Trp Tyr Gln Pro Tyr Ser Val Gln Arg
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Val His Val Tyr Trp Gln Pro Tyr Ser Val Gln Arg

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Gln Ala Arg Trp Tyr Gln Pro Tyr Ser Val Gln Arg
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Val His Val Tyr Trp Gln Pro Tyr Ser Val Gln Thr
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Arg Ser Val Tyr Trp Gln Pro Tyr Ser Val Gln Arg
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Gly Arg Ile Trp Phe Gln Pro Tyr Ser Val Gln Arg
1 5 10

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Ala Arg Thr Trp Tyr Gln Pro Tyr Ser Val Gln Arg

1 5 10

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Ala Arg Val Trp Trp Gln Pro Tyr Ser Val Gln Met

1 5 10

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Arg Leu Met Phe Tyr Gln Pro Tyr Ser Val Gln Arg
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Glu Ser Met Trp Tyr Gln Pro Tyr Ser Val Gln Arg
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Arg Leu Val Tyr Trp Gln Pro Tyr Ala Pro Ile Tyr

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1 5 10

<210> 720

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<211> 12

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Arg Leu Val Tyr Trp Gln Pro Tyr Ser Tyr Gln Thr

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<400> 721

Arg Leu Val Tyr Trp Gln Pro Tyr Ser Leu Pro Ile
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<400> 722

Arg Leu Val Tyr Trp Gln Pro Tyr Ser Val Gln Ala

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 Ser Arg Val Trp Tyr Gln Pro Tyr Ala Lys Gly Leu
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 Ser Arg Val Trp Tyr Gln Pro Tyr Ala Met Pro Leu
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Ser Arg Val Trp Tyr Gln Pro Tyr Ser Leu Gly Leu
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Ser Arg Val Trp Tyr Gln Pro Tyr Ala Arg Glu Leu
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 Ser Arg Val Trp Tyr Gln Pro Tyr Phe Val Gln Pro
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 Glu Tyr Glu Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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<223> Description of Artificial Sequence: IL-1 ANTAGONIST

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PEPTIDE

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Ile Pro Glu Tyr Trp Gln Pro Tyr Ala Leu Pro Leu
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Ser Arg Ile Trp Trp Gln Pro Tyr Ala Leu Pro Leu
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Asp Pro Leu Phe Trp Gln Pro Tyr Ala Leu Pro Leu
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<400> 735 Ser Arg Gln Trp Val Gln Pro Tyr Ala Leu Pro Leu

PEPTIDE

1 5 10

<210> 736

<211> 12

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<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

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Ile Arg Ser Trp Trp Gln Pro Tyr Ala Leu Pro Leu
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<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

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Arg Gly Tyr Trp Gln Pro Tyr Ala Leu Pro Leu
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<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

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Arg Leu Leu Trp Val Gln Pro Tyr Ala Leu Pro Leu
1 5 10

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Asp Ala Tyr Trp Val Gln Pro Tyr Ala Leu Pro Leu
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Trp Ser Gly Tyr Phe Gln Pro Tyr Ala Leu Pro Leu
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<210> 742 <211> 12

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Asn Ile Glu Phe Trp Gln Pro Tyr Ala Leu Pro Leu
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Thr Arg Asp Trp Val Gln Pro Tyr Ala Leu Pro Leu
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      PEPTIDE
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Asp Ser Ser Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
1 5 10

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 Ile Gly Asn Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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 Asn Leu Arg Trp Asp Gln Pro Tyr Ala Leu Pro Leu
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 Leu Pro Glu Phe Trp Gln Pro Tyr Ala Leu Pro Leu
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                  5
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PEPTIDE

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Asp Ser Tyr Trp Trp Gln Pro Tyr Ala Leu Pro Leu
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Arg Ser Gln Tyr Tyr Gln Pro Tyr Ala Leu Pro Leu -
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Ala Arg Phe Trp Leu Gln Pro Tyr Ala Leu Pro Leu
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      PEPTIDE
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Asn Ser Tyr Phe Trp Gln Pro Tyr Ala Leu Pro Leu

<400> 751

1 5 10

<210> 752

<211> 12

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<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

<400> 752

Arg Phe Met Tyr Trp Gln Pro Tyr Ser Val Gln Arg
1 5 10

<210> 753

<211> 12

<212> PRT

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<220>

<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

<400> 753

Ala His Leu Phe Trp Gln Pro Tyr Ser Val Gln Arg
1 5 10

<210> 754

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

<400> 754

Trp Trp Gln Pro Tyr Ala Leu Pro Leu

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 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
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 Tyr Tyr Gln Pro Tyr Ala Leu Pro Leu
           5
 <210> 756
<211> 9 · · · · ·
 <212> PRT
 <213> Artificial Sequence
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       PEPTIDE
 <400> 756
 Tyr Phe Gln Pro Tyr Ala Leu Gly Leu
                 5
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 <211> 10
 <212> PRT
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       PEPTIDE
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 Tyr Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
                                     10
             5
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<210> 758 <211> 10

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Arg Trp Trp Gln Pro Tyr Ala Thr Pro Leu
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<211> 10
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Gly Trp Tyr Gln Pro Tyr Ala Leu Gly Phe
                5
<210> 760
<211> 10
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Tyr Trp Tyr Gln Pro Tyr Ala Leu Gly Leu
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<210> 761 <211> 10 <212> PRT <213> Artificial Sequence

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Ile Trp Tyr Gln Pro Tyr Ala Met Pro Leu
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Ser Asn Met Gln Pro Tyr Gln Arg Leu Ser
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Thr Phe Val Tyr Trp Gln Pro Tyr Ala Val Gly Leu Pro Ala Ala Glu
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                                     10
                  5
Thr Ala Cys Asn
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WO 00/24782 <220> <223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE <400> 764 Thr Phe Val Tyr Trp Gln Pro Tyr Ser Val Gln Met Thr Ile Thr Gly 10 Lys Val Thr Met 20 <210> 765 <211> 20 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE <400> 765 Thr Phe Val Tyr Trp Gln Pro Tyr Ser Ser His Xaa Xaa Val Pro Xaa 10 15 5 Gly Phe Pro Leu 20 <210> 766 <211> 20

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

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Thr Phe Val Tyr Trp Gln Pro Tyr Tyr Gly Asn Pro Gln Trp Ala Ile 10 5

His Val Arg His ... 20

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Thr Phe Val Tyr Trp Gln Pro Tyr Val Leu Leu Glu Leu Pro Glu Gly
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Ala Val Arg Ala
<210> 768
<211> 20
<212> PRT
<213> Artificial Sequence
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Thr Phe Val Tyr Trp Gln Pro Tyr Val Asp Tyr Val Trp Pro Ile Pro
                  5
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Ile Ala Gln Val
<210> 769
<211> 11
<212> PRT
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<400> 769
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Gly Trp Tyr Gln Pro Tyr Val Asp Gly Trp Arg

5 10

<210> 770

<211> 12

<212> PRT

<213> Artificial Sequence

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<400> 770 ·

Arg Trp Glu Gln Pro Tyr Val Lys Asp Gly Trp Ser
1 5 10

<210> 771

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<400> 771

Glu Trp Tyr Gln Pro Tyr Ala Leu Gly Trp Ala Arg

1 5 10

<210> 772

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<400> 772

Gly Trp Trp Gln Pro Tyr Ala Arg Gly Leu
1 5 10

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Leu Phe Glu Gln Pro Tyr Ala Lys Ala Leu Gly Leu
                  5
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Gly Trp Glu Gln Pro Tyr Ala Arg Gly Leu Ala Gly
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<210> 775
<211> 12
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      PEPTIDE
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Ala Trp Val Gln Pro Tyr Ala Thr Pro Leu Asp Glu
                                     10
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<210> 776 <211> 12

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Met Trp Tyr Gln Pro Tyr Ser Ser Gln Pro Ala Glu
                                     10
                  5
<210> 777
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Gly Trp Thr Gln Pro Tyr Ser Gln Gln Gly Glu Val
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Asp Trp Phe Gln Pro Tyr Ser Ile Gln Ser Asp Glu
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<210> 779 <211> 11 <212> PRT
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Pro Trp Ile Gln Pro Tyr Ala Arg Gly Phe Gly
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Arg Pro Leu Tyr Trp Gln Pro Tyr Ser Val Gln Val
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Thr Leu Ile Tyr Trp Gln Pro Tyr Ser Val Gln Ile
                5
  1
<210> 782
<211> 12
<212> PRT
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PEPTIDE

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Trp His Gln Phe Val Gln Pro Tyr Ala Leu Pro Leu
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Glu Trp Asp Ser Val Tyr Trp Gln Pro Tyr Ser Val Gln Thr Leu Leu
                                     10
Arg
<210> 785
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      PEPTIDE
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<400> 785
Trp Glu Gln Asn Val Tyr Trp Gln Pro Tyr Ser Val Gln Ser Phe Ala
1 5 10 15

Asp

<210> 786

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

<400> 786

Ser Asp Val Val Tyr Trp Gln Pro Tyr Ser Val Gln Ser Leu Glu Met

1 5 10 15

<210> 787

<211> 17

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

<400> 787

Tyr Tyr Asp Gly Val Tyr Trp Gln Pro Tyr Ser Val Gln Val Met Pro 1 5 10 15

Ala

<210> 788

<211> 12

<212> PRT

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 Ser Asp Ile Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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  Gln Arg Ile Trp Trp Gln Pro Tyr Ala Leu Pro Leu
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  Ser Arg Ile Trp Trp Gln Pro Tyr Ala Leu Pro Leu
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  <213> Artificial Sequence
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<223> Description of Artificial Sequence: IL-1 ANTAGONIST

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PEPTIDE

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Arg Ser Leu Tyr Trp Gln Pro Tyr Ala Leu Pro Leu
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Thr Ile Ile Trp Glu Gln Pro Tyr Ala Leu Pro Leu
                                     10
                  5
  1
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Trp Glu Thr Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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                  5
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      PEPTIDE
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Ser Tyr Asp Trp Glu Gln Pro Tyr Ala Leu Pro Leu

1 5 10

<210> 795

<211> 12

<212> PRT

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<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

<400> 795

Ser Arg Ile Trp Cys Gln Pro Tyr Ala Leu Pro Leu 1 5 10

<210> 796

<211> 12

<212> PRT

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<400> 796

Glu Ile Met Phe Trp Gln Pro Tyr Ala Leu Pro Leu 1 5 10

<210> 797

<211> 12

<212> PRT

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<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

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Gly Ser Lys Val Ile Leu Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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Arg Gln Gly Ala Asn Ile Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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                   5
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<210> 801 <211> 15

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Gly Gly Gly Asp Glu Pro Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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<210> 802 .

<211> 15

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Ser Gln Leu Glu Arg Thr Trp Tyr Gln Pro Tyr Ala Leu Pro Leu 1 5 10 15

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Glu Thr Trp Val Arg Glu Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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Lys Lys Gly Ser Thr Gln Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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<211> 15

<212> PRT

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Val Lys Gln Lys Trp Arg Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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<210> 808

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Leu Arg Arg His Asp Val Trp Tyr Gln Pro Tyr Ala Leu Pro Leu

1 5 10 15

<210> 809

<211> 15

<212> PRT

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<212> PRT

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1 5 10 15

<210> 811

<211> 15

<212> PRT

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<211> 15

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<400> 813

Val Ile Glu Trp Trp Gln Pro Tyr Ala Leu Pro Leu

1 5 10

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Ala Ser Glu Trp Trp Gln Pro Tyr Ala Leu Pro Leu
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 Phe Tyr Glu Trp Trp Gln Pro Tyr Ala Leu Pro Leu
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<210> 817 <211> 12

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Trp Gly Glu Trp Leu Gln Pro Tyr Ala Leu Pro Leu
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                  5
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Phe Ile Glu Trp Phe Gln Pro Tyr Ala Leu Pro Leu
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                   5
  1
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PEPTIDE

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                 5
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 Asn Xaa Xaa Trp Xaa Xaa Pro Tyr Ala Leu Pro Leu
                                   10
                 5
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Trp Gly Asn Trp Tyr Gln Pro Tyr Ala Leu Pro Leu

<400> 826

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10 5 1

<210> 827

<211> 12

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Thr Leu Tyr Trp Glu Gln Pro Tyr Ala Leu Pro Leu 5

<210> 828

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<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

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Val Trp Arg Trp Glu Gln Pro Tyr Ala Leu Pro Leu 10

<210> 829

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Leu Leu Trp Thr Gln Pro Tyr Ala Leu Pro Leu 5

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Ser Arg Ile Trp Xaa Xaa Pro Tyr Ala Leu Pro Leu
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<210> 833 <211> 12

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Thr Ser Gly Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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<212> PRT
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Val His Pro Tyr Xaa Xaa Pro Tyr Ala Leu Pro Leu
<210> 835
<211> 12
<212> PRT
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 Glu His Ser Tyr Phe Gln Pro Tyr Ala Leu Pro Leu
                   5
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<210> 836 <211> 12" <212> PRT <213> Artificial Sequence

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Xaa Xaa Ile Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
                  5
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Ala Gln Leu His Ser Gln Pro Tyr Ala Leu Pro Leu
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Trp Ala Asn Trp Phe Gln Pro Tyr Ala Leu Pro Leu
                   5
<210> 839
<211> 12
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PEPTIDE

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Ser Arg Leu Tyr Ser Gln Pro Tyr Ala Leu Pro Leu
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Gly Val Thr Phe Ser Gln Pro Tyr Ala Leu Pro Leu
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Ser Ile Val Trp Ser Gln Pro Tyr Ala Leu Pro Leu
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 Ser Arg Asp Leu Val Gln Pro Tyr Ala Leu Pro Leu
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1 5 10

<210> 843

<211> 17

<212> PRT

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<220>

<400> 843

His Trp Gly His Val Tyr Trp Gln Pro Tyr Ser Val Gln Asp Asp Leu

1 5 10 15

Gly

<210> 844

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

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<400> 844

Ser Trp His Ser Val Tyr Trp Gln Pro Tyr Ser Val Gln Ser Val Pro 1 5 10 15

Glu

<210> 845

<211> 17

<212> PRT

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<210> 848 <211> 17

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Tyr Trp Ser Ser Val Tyr Trp Gln Pro Tyr Ser Val Gln Ser Val His
1
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                  5
Ser
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Tyr Trp Tyr Gln Pro Tyr Ala Leu Gly Leu
                 5
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Tyr Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
                   5
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<210> 851 <211> 10

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Glu Trp Ile Gln Pro Tyr Ala Thr Gly Leu
<210> 852
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Asn Trp Glu Gln Pro Tyr Ala Lys Pro Leu
<210> 853
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Ala Phe Tyr Gln Pro Tyr Ala Leu Pro Leu
<210> 854
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<211> 10 --- <212> PRT

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 Phe Leu Tyr Gln Pro Tyr Ala Leu Pro Leu
                  5
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 Val Cys Lys Gln Pro Tyr Leu Glu Trp Cys
                   5
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 Glu Thr Pro Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
 Tyr Ala Leu Pro Leu
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<213> Artificial Sequence

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PEPTIDE

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Tyr Ala Leu Pro Leu 20

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<210> 860
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Asp Gly Tyr Asp Arg Trp Arg Gln Ser Gly Glu Arg Tyr Trp Gln Pro
                                     10
Tyr Ala Leu Pro Leu
             20
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       PEPTIDE
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Thr Ala Asn Val Ser Ser Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro
                                                           15
                                      10
                  5
 Tyr Ala Leu Pro Leu
              20
 <210> 862
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<400> 862 Ser Val Gly Glu Asp His Asn Phe Trp Thr Ser Glu Tyr Trp Gln Pro

PEPTIDE

1 5 10 15

Tyr Ala Leu Pro Leu 20

<210> 863

<211> 21

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

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Met Asn Asp Gln Thr Ser Glu Val Ser Thr Phe Pro Tyr Trp Gln Pro 1 5 10 15

Tyr Ala Leu Pro Leu 20

<210> 864

<211> 21

<212> PRT

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<220>

<400> 864

Ser Trp Ser Glu Ala Phe Glu Gln Pro Arg Asn Leu Tyr Trp Gln Pro 1 5 10 15

Tyr Ala Leu Pro Leu 20

<210> 865

<211> 21 ...

<212> PRT

<213> Artificial Sequence

<220>

<400> 865

Gln Tyr Ala Glu Pro Ser Ala Leu Asn Asp Trp Gly Tyr Trp Gln Pro 1 5 10 15

Tyr Ala Leu Pro Leu

20

<210> 866

<211> 21

<212> PRT

<213> Artificial Sequence

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<400> 866

Asn Gly Asp Trp Ala Thr Ala Asp Trp Ser Asn Tyr Tyr Trp Gln Pro 1 5 10 15

Tyr Ala Leu Pro Leu

20

<210> 867

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<212> PRT

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Thr His Asp Glu His Ile Tyr Trp Gln Pro Tyr Ala Leu Pro Leu

1 5 10 15

<210> 868

<211> 21

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 Tyr Ala Leu Pro Leu
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                                                          15
   1
                   5
 Ala Leu Pro Leu
              20
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                                                          15
                                     10
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Tyr Ala Leu Pro Leu

20

<210> 871

<211> 21

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<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

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Gly Asp Asp Ala Ala Trp Arg Thr Asp Ser Leu Thr Tyr Trp Gln Pro 1 5 10 15

Tyr Ala Leu Pro Leu 20

<210> 872

<211> 21

<212> PRT

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<400> 872

Ala Ile Ile Arg Gln Leu Tyr Arg Trp Ser Glu Met Tyr Trp Gln Pro 1 5 10 15

Tyr Ala Leu Pro Leu

20

<210> 873

<211> 21

<212> PRT

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<220>

<400> 873

Glu Asn Thr Tyr Ser Pro Asn Trp Ala Asp Ser Met Tyr Trp Gln Pro 1 5 10 15

Tyr Ala Leu Pro Leu

20

<210> 874

<211> 21

<212> PRT

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Met Asn Asp Gln Thr Ser Glu Val Ser Thr Phe Pro Tyr Trp Gln Pro 1 5 10 15

Tyr Ala Leu Pro Leu 20

<210> 875

<211> 21

<212> PRT

<213> Artificial Sequence

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<400> 875

Ser Val Gly Glu Asp His Asn Phe Trp Thr Ser Glu Tyr Trp Gln Pro 1 5 10 15

Tyr Ala Leu Pro Leu

20

<210> 876

<211> 21

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<212> PRT
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                 5
Tyr Ala Leu Pro Leu
             20
<210> 877
<211> 21
<212> PRT
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<220>

<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

<400> 877

Glu Asn Pro Phe Thr Trp Gln Glu Ser Asn Ala Tyr Tyr Trp Gln Pro 15 5 10

Tyr Ala Leu Pro Leu 20

<210> 878 <211> 21 <212> PRT <213> Artificial Sequence

<220> <223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

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Tyr Ala Leu Pro Leu

20

<210> 879 <211> 21

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

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Gln Ile Pro Phe Thr Trp Glu Gln Ser Asn Ala Tyr Tyr Trp Gln Pro 1 5 10 15

Tyr Ala Leu Pro Leu 20

<210> 880

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<400> 880

Gln Ala Pro Leu Thr Trp Gln Glu Ser Ala Ala Tyr Tyr Trp Gln Pro 1 5 10 15

Tyr Ala Leu Pro Leu

20

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<211> 21

<212> PRT

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Tyr Ala Leu Pro Leu

20

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Tyr Ala Leu Pro Leu 20

<210> 886 <211> 21 <212> PRT <213> Artificial Sequence

<220> <223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

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Tyr Ala Leu Pro Leu

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<210> 887

<211> 20

<212> PRT

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<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

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Ser Thr Pro Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro Tyr 1 5 10 15

Ala Leu Pro Leu

<210> 888

<211> 21

<212> PRT

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<223> Description of Artificial Sequence:IL-1 ANTAGONIST
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Glu Thr Pro Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro 1 5 10 15

Tyr Ala Leu Pro Leu 20

<210> 889

<211> 21

<212> PRT

<213> Artificial Sequence

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<400> 889 Lys Ala Pro Phe Thr Trp Glu Glu Ser Gln Ala Tyr Tyr Trp Gln Pro 10 5 Tyr Ala Leu Pro Leu 20 <210> 890 <211> 21 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE <400> 890 Ser Thr Ser Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro 10 15 Tyr Ala Leu Pro Leu 20

<210> 891 <211> 21 <212> PRT <213> Artificial Sequence

<220> <223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

Asp Ser Thr Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro 10 5

Tyr Ala Leu Pro Leu 20

<210> 892 <211> 21

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<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:IL-1 ANTAGONIST
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<400> 892

Tyr Ile Pro Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro 1 .5 10 15

Tyr Ala Leu Pro Leu 20

<210> 893 <211> 21 <212> PRT <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

<400> 893

Gln Thr Ala Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro 1 5 10 15

Tyr Ala Leu Pro Leu 20

<210> 894 <211> 21 <212> PRT <213> Artificial Sequence

<400> 894
Glu Thr Leu Phe Thr Trp Glu Glu Ser Asn Ala Thr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu

20

```
<210> 895
<211> 21
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 895
Val Ser Ser Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
                                      10
Tyr Ala Leu Pro Leu
             20
<210> 896
<211> 7
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 896
Gln Pro Tyr Ala Leu Pro Leu
<210> 897
<211> 11
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 1, Xaa is a phosphotyrosyl residue
```

```
<220>
<223> At position 2, Xaa is a 1-napthylalanyl residue
<223> At position 6, Xaa is an azetidine residue
<400> 897
Xaa Xaa Pro Tyr Gln Xaa Tyr Ala Leu Pro Leu
<210> 898
<211> 21
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
     PEPTIDE
<400> 898
Thr Ala Asn Val Ser Ser Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro
                                                         15
                                    10
Tyr Ala Leu Pro Leu
             20
<210> 899
<211> 15
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr Ala Leu Pro Leu
                                                         15
                                     10
                 5
```

<210> 900 <211> 15

```
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 10, Xaa is an azetidine residue
Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr Ala Leu Pro Leu
                  5
                                    10
<210> 901
<211> 15
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 901
Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr Ala Leu Pro Leu
                                    10
                 5
<210> 902
<211> 21
<212> PRT
<213> Artificial Sequence
<220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
 <400> 902
 Glu Thr Pro Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
```

Tyr Ala Leu Pro Leu

.5

10

20

PEPTIDE

Pro Leu

```
<210> 905
<211> 17
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:IL-1 ANTAGONIST
```

```
<400> 905
 Gly Asp Val Ala Glu Tyr Trp Gln Pro Tyr Ala Leu Pro Leu Thr Ser
                                      10
 Leu
 <210> 906
 <211> 18
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <400> 906
 Ser Trp Thr Asp Tyr Gly Tyr Trp Gln Pro Tyr Ala Leu Pro Ile Ser
                   5
 Gly Leu
 <210> 907
 <211> 8
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
  <223> At position 4, Xaa is prolyl or an azetidine
        residue
  <220>
  <223> At position 6, Xaa is S, A, V or L
  <400> 907
  Xaa Xaa Gln Xaa Tyr Xaa Xaa Xaa
                   5
```

```
<210> 908
<211> 8
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 1, Xaa is Y, W or F
<220>
<223> At position 4, Xaa is prolyl or an azetidine
     residue
<220>
<223> At position 6, Xaa is S, A, V or L
<400> 908
Xaa Xaa Gln Xaa Tyr Xaa Xaa Xaa
                 5
  1 .
<210> 909
<211> 8
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 1, Xaa is Y, W or F
 <220>
 <223> At position 2, Xaa is E, F, V, W or Y
 <220>
 <223> At position 4, Xaa is prolyl or an azetidine
       residue
 <220>
 <223> At position 6, Xaa is S, A, V or L
```

```
<220>
```

<223> At position 7, Xaa is M, F, V, R, Q, K, T, S, D, L, I or E

<220>

<223> At position 8, Xaa is E, L, W, V, H, I, G, A, D, L, Y, N, Q or P

<400> 909

Xaa Xaa Gln Xaa Tyr Xaa Xaa Xaa 1 5

<210> 910

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

<220>

<223> At position 1, Xaa is V, L, I, E, P, G, Y, M, T or D

<220>

<223> At position 2, Xaa is Y, W or F

<220>

<223> At position 3, Xaa is E, F, V, W or Y

<220>

<223> At position 5, Xaa is prolyl or an azetidine residue

<220>

<223> At position 7, Xaa is S, A, V or L

<220>

<223> At position 8, Xaa is M, F, V, R, Q, K, T, S, D, L, I or E

<220>

<223> At position 9, Xaa is E, L, W, V, H, I, G, A, D,
 L, Y, N, Q or P

<400> 910 Xaa Xaa Xaa Gln Xaa Tyr Xaa Xaa Xaa 1 5 <210> 911 <211> 15 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE <400> 911 Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr Ala Leu Pro Leu 10 5 <210> 912 <211> 15 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE <220> <223> At position 10, Xaa is an azetidine residue <400> 912 Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr Ala Leu Pro Leu 15 10 5 <210> 913 <211> 15 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: IL-1 ANTAGONIST

PEPTIDE

```
<400> 913
Phe Glu Trp Thr Pro Gly Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
                 5
                                    10
<210> 914
<211> 15
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 914
Phe Glu Trp Thr Pro Gly Trp Tyr Gln Xaa Tyr Ala Leu Pro Leu
                                                        15
                                    10
<210> 915
<211> 15
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 915
Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Pro Tyr Ala Leu Pro Leu
                                10
                  5
 <210> 916
 <211> 15
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
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PEPTIDE

<220>

<223> At position 10, Xaa is an azetidine residue

<400> 916

Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 917

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

<220>

<223> At position 1, Xaa is A, D, E, F, G, K, Q, S, T, V or Y

<220>

<223> At position 2, Xaa is A, D, G, I, N, P, S, T, V or W

<220>

<223> At position 3, Xaa is A, D, G, L, N, P, S, T, W or Y

<220>

<223> At position 4, Xaa is A, D, E, F, L, N, R, V or Y

<220>

<223> At position 5, Xaa is A, D, E, Q, R, S or T

<220>

<223> At position 6, Xaa is H, I, L, P, S, T or W

<220>

<223> At position 7, Xaa is A, E, F, K, N, Q, R, S or Y

<220×

<223> At position 8, Xaa is D, E, F, Q, R, T or W

<220>

<223> At position 9, Xaa is A, D, P, S, T or W

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<220>
<223> At position 10, Xaa is A, D, G, K, N, Q, S or T
<220>
<223> At position 11, Xaa is A, E, L, P, S, T, V or Y
<220>
<223> At position 12, Xaa is V, L, I, E, P, G, Y, M, T
     or D
<220>
<223> At position 13, Xaa is Y, W or F
<220>
<223> At position 14, Xaa is E, F, V, W or Y
<220>
<223> At position 16, Xaa is P or an azetidine residue
<223> At position 18, Xaa is S, A, V or L
<223> At position 19, Xaa is M, F, V, R, Q, K, T, S, D,
     L, I or E
<220>
<223> At position 20, Xaa is Q or P
<400> 917
15
                                  10
                 5
  1
Tyr Xaa Xaa Xaa Leu
<210> 918
<211> 21
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:IL-1 ANTAGONIST
      PEPTIDE
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<210> 919
<211> 18
<212> PRT
<213> Artificial Sequence
<220>

<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

Gly Leu

<210> 920 <211> 21 <212> PRT <213> Artificial Sequence

Tyr Ala Leu Pro Leu 20

<210> 921 <211> 21 <212> PRT

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<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
     PEPTIDE
<400> 921
Glu Asn Thr Tyr Ser Pro Asn Trp Ala Asp Ser Met Tyr Trp Gln Pro
  1 5 10
Tyr Ala Leu Pro Leu
            20
<210> 922
<211> 21
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 922
Ser Val Gly Glu Asp His Asn Phe Trp Thr Ser Glu Tyr Trp Gln Pro
                                                       15
                                    10
Tyr Ala Leu Pro Leu
             20
 <210> 923
 <211> 21
 <212> PRT
 <213> Artificial Sequence
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
 <400> 923
 Asp Gly Tyr Asp Arg Trp Arg Gln Ser Gly Glu Arg Tyr Trp Gln Pro
```

Tyr Ala Leu Pro Leu 20

5

10

15

```
<210> 924
 <211> 15
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <400> 924
 Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr Ala Leu Pro Leu
                  5
                                     10
 <210> 925
 <211> 13
 <212> PRT
<213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <400> 925
 Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr Asn His
                                     10
                   5
 <210> 926
 <211> 13
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <223> At position 10, Xaa is an azetidine residue
 <400> 926 ···
 Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr Asn His
                    5
```

```
<210> 927
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 927
Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr Asn His
                 5
<210> 928
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:IL-1 ANTAGONIST
     PEPTIDE
<223> At position 10, Xaa is an azetidine residue
<400> 928
Phe Glu Trp Thr Pro Gly Trp Tyr Gln Xaa Tyr
<210> 929
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 10, Xaa is an azetidine residue
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```
<400> 929
Ala Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
                  5
<210> 930
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
     PEPTIDE
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 930
Phe Ala Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
                  5
<210> 931
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
 <220>
 <223> At position 10, Xaa is an azetidine residue
 <400> 931
 Phe Glu Ala Thr Pro Gly Tyr Trp Gln Xaa Tyr
                   5
 <210> 932
 <211> 11
 <212> PRT
```

<213> Artificial Sequence

<220>

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<223> Description of Artificial Sequence: IL-1 ANTAGONIST
     PEPTIDE
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 932
Phe Glu Trp Ala Pro Gly Tyr Trp Gln Xaa Tyr
<210> 933
<211> 11
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence:IL-1 ANTAGONIST
    PEPTIDE
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 933
Phe Glu Trp Thr Ala Gly Tyr Trp Gln Xaa Tyr
          5
<210> 934
<211> 11
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 934
Phe Glu Trp Thr Pro Ala Tyr Trp Gln Xaa Tyr
                  5
```

```
<210> 935
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 935
Phe Glu Trp Thr Pro Gly Ala Trp Gln Xaa Tyr
                  5
<210> 936
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 936
Phe Glu Trp Thr Pro Gly Tyr Ala Gln Xaa Tyr
                  5
<210> 937
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <223> At position 10, Xaa is an azetidine residue
```

```
<400> 937
Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Ala
1 5 10
```

<210> 938

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<220>

<223> At position 10, Xaa is an azetidine residue

<400> 938

Phe Glu Trp Thr Gly Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 939

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<220>

<223> At position 5, D amino acid residue

<220>

<223> At position 10, Xaa is an azetidine residue

<400> 939

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 940

<211> 10

<212> PRT

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<213> Artificial Sequence
<220>
<223> Description of Arti
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<223> Description of Artificial Sequence:IL-1 ANTAGONIST
 PEPTIDE

<220>

<223> At position 10, Xaa is an azetidine residue

<400> 940

Phe Glu Trp Thr Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 941

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

<220>

<223> At position 5, Xaa is a pipecolic acid residue

<220>

<223> At position 10, Xaa is an azetidine residue

<400> 941

Phe Glu Trp Thr Xaa Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 942

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<220>

<223> At position 6, Xaa is an aminoisobutyric acid residue

```
<220>
 <223> At position 10, Xaa is an azetidine residue
 Phe Glu Trp Thr Pro Xaa Tyr Trp Gln Xaa Tyr
                   5
 <210> 943
 <211> 11
 <212> PRT
 <213> Artificial Sequence
 <220>
  <223> Description of Artificial Sequence: IL-1 ANTAGONIST
        PEPTIDE
  <220>
  <223> At position 6, Xaa is a sarcosine residue
  <223> At position 10, Xaa is an azetidine residue
  <400> 943
  Phe Glu Trp Thr Pro Xaa Trp Tyr Gln Xaa Tyr
                                       10
                    5
  <210> 944
  <211> 11
  <212> PRT
<213> Artificial Sequence
  <220>
  <223> Description of Artificial Sequence: IL-1 ANTAGONIST
        PEPTIDE
  <220>
  <223> At position 5, Xaa is a sarcosine residue
  <220>
  <223> At position 10, Xaa is an azetidine residue
  <400> 944
  Phe Glu Trp Thr Xaa Gly Tyr Trp Gln Xaa Tyr
```

1 5 10

<210> 945

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST
PEPTIDE

<220>

<223> At position 10, Xaa is an azetidine residue

<400> 945

Phe Glu Trp Thr Pro Asn Tyr Trp Gln Xaa Tyr
1 5 10

<210> 946

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST
 PEPTIDE

<220>

<223> At position 5, D amino acid residue

<220>

<223> At position 10, Xaa is an azetidine residue

<400> 946

Phe Glu Trp Thr Pro Val Tyr Trp Gln Xaa Tyr 1 5 10

<210> 947

<211> 11 ...

<212> PRT

<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 947
Phe Glu Trp Thr Val Pro Tyr Trp Gln Xaa Tyr
                 5
<210> 948
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 1, Xaa is acetylated phe
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 948
Phe Glu Trp Thr Pro Gly Trp Tyr Gln Xaa Tyr
                 5
<210> 949
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 1, Xaa is acetylated phe
```

<223> At position 10, Xaa is an azetidine residue

<220>

```
<400> 949
Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
 1
                  5
<210> 950
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 1, Xaa=1-naphthylalanine
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 950
Xaa Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr
<210> 951
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<223> At position 10, Xaa is an azetidine residue
Tyr Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr
                 5
 1
```

<210> 952 <211> 11 <212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

<220>

<223> At position 10, Xaa is an azetidine residue

<400> 952

Phe Glu Trp Val Pro Gly Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 953

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<220>

<223> At position 10, Xaa is an azetidine residue

<400> 953

Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 954

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST
 PEPTIDE

<220>

<223> At position 10, Xaa is an azetidine residue

<400> 954

Phe Glu Trp Thr Pro Ser Tyr Tyr Gln Xaa Tyr

1 5 10

<210> 955 <211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

<220>

<223> At position 10, Xaa is an azetidine residue

<400> 955

Phe Glu Trp Thr Pro Asn Tyr Tyr Gln Xaa Tyr

1 5 10

<210> 956

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST
 PEPTIDE

<220>

<223> At position 5, Xaa=naphthylalanine

<400> 956

Ser His Leu Tyr Xaa Gln Pro Tyr Ser Val Gln Met
1 5 10

<210> 957

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

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<220>
<223> At position 5, Xaa=naphthylalanine
<400> 957
Thr Leu Val Tyr Xaa Gln Pro Tyr Ser Leu Gln Thr
  1
                  5
<210> 958
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 5, Xaa=naphthylalanine
<400> 958
Arg Gly Asp Tyr Xaa Gln Pro Tyr Ser Val Gln Ser
                  5
                                     10
  1
<210> 959
<211> 12
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 5, Xaa=naphthylalanine
<400> 959
Asn Met Val Tyr Xaa Gln Pro Tyr Ser Ile Gln Thr
                                      10
  1
                   5
```

<210> 960 <211> 9

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<212> PRT
  <213> Artificial Sequence
  <220>
  <223> Description of Artificial Sequence: IL-1 ANTAGONIST
        PEPTIDE
  <400> 960
  Val Tyr Trp Gln Pro Tyr Ser Val Gln
  <210> 961
<211> 9
  <212> PRT
  <213> Artificial Sequence
  <220>
  <223> Description of Artificial Sequence: IL-1 ANTAGONIST
        PEPTIDE
  <220>
  <223> At position 3, Xaa=naphthylalanine
  <400> 961
  Val Tyr Xaa Gln Pro Tyr Ser Val Gln
                   5
  <210> 962
  <211> 12
  <212> PRT
  <213> Artificial Sequence
  <220>
  <223> Description of Artificial Sequence: IL-1 ANTAGONIST
        PEPTIDE
  <223> At position 7, Xaa is an azetidine residue
  <400> 962
  Thr Phe Val Tyr Trp Gln Xaa Tyr Ala Leu Pro Leu
                    5
```

```
<210> 963
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 10, Xaa is an azetidine residue
<220>
<223> At position 11, Xaa =p-benzoyl-L-phenylalanine
<400> 963
Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Xaa
                  5
<210> 964
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 1, Xaa=acetylated phe
<220>
<223> At position 10, Xaa is an azetidine residue
 <223> At position 11, Xaa=p-benzoyl-L-phenylalanine
 <400> 964
 Xaa Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Xaa
                                      10
                   5
  1
```

<210> 965 <211> 11

```
<212> PRT
```

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

<220>

<223> At position 8, Xaa=p-benzoyl-L-phenylalanine

<220>

<223> At position 10, Xaa is an azetidine residue

<400> 965

Phe Glu Trp Thr Pro Gly Tyr Xaa Gln Xaa Tyr
1 5 10

<210> 966

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<220>

<223> At position 1, Xaa=acetylated phe

<220>

<223> At position 8, Xaa=p-benzoyl-L-phenylalanine

<2202

<223> At position 10, Xaa is an azetidine residue

<400> 966

Phe Glu Trp Thr Pro Gly Tyr Xaa Gln Xaa Tyr
1 5 10

<210> 967

<211> 11

<212> PRT ---

<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 7, Xaa=p-benzoyl-L-phenylalanine
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 967
Phe Glu Trp Thr Pro Gly Xaa Tyr Gln Xaa Tyr
                  5
<210> 968
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 1, Xaa=acetylated phe
<220>
<223> At position 7, Xaa=p-benzoyl-L-phenylalanine
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 968
Phe Glu Trp Thr Pro Gly Xaa Tyr Gln Xaa Tyr
                                     10
                  5
  1
<210> 969
<211> 11
<212> PRT
```

```
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:IL-1 ANTAGONIST
PEPTIDE
```

```
<220>
<223> At position 1, Xaa=acetylated phe
<220>
<223> At position 3, Xaa=p-benzoyl-L-phenylalanine
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 969
Phe Glu Xaa Thr Pro Gly Tyr Tyr Gln Xaa Tyr
                  5
<210> 970
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 1, Xaa=acetylated phe
<220>
<223> At position 3, Xaa=p-benzoyl-L-phenylalanine
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 970
Phe Glu Xaa Thr Pro Gly Tyr Tyr Gln Xaa Tyr
                  5
                                      10
<210> 971
<211> 11
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
```

```
<220>
<223> At position 1, Xaa=p-benzoyl-L-phenylalanine
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 971
Xaa Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr
<210> 972
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 1, Xaa=acetylated
      p-benzoyl-L-phenylalanine
<220>
<223> At position 10, Xaa is an azetidine residue
<400> 972
Xaa Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr
                  5
<210> 973
<211> 9
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 973
Val Tyr Trp. Gln Pro Tyr Ser Val Gln
                  5
  1
```

```
<210> 974
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 974
Arg Leu Val Tyr Trp Gln Pro Tyr Ser Val Gln Arg
                5
<210> 975
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 5, Xaa=naphthylalanine
Arg Leu Val Tyr Xaa Gln Pro Tyr Ser Val Gln Arg
                  5
                                     10
<210> 976
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 976
Arg Leu Asp Tyr Trp Gln Pro Tyr Ser Val Gln Arg
  1
                  5
```

```
<210> 977
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 977
Arg Leu Val Trp Phe Gln Pro Tyr Ser Val Gln Arg
                   5
                                      10
  1
<210> 978
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
<400> 978
Arg Leu Val Tyr Trp Gln Pro Tyr Ser Ile Gln Arg
  1
                  5
<210> 979
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <220>
 <223> At position 1, Xaa=D or Y
 <220>
 <223> At position 3, Xaa=D or S
 <220>
```

```
<223> At position 4, Xaa=S, T or A
<220>
<223> At position 5, Xaa=S or W
<220>
<223> At position 6, Xaa=S or Y
<220>
<223> At position 7, Xaa=D, Q, E or V
<223> At position 8, Xaa=N, S, K, H or W
<223> At position 9, Xaa=F or L
<220>
<223> At position 10, Xaa=D, N, S or L
<220>
<223> At position 11, Xaa=L, I, Q, M or A
<400> 979
Xaa Asn Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                  5
<210> 980
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:IL-1 ANTAGONIST
      PEPTIDE
<400> 980
Asp Asn Ser Ser Trp Tyr Asp Ser Phe Leu Leu
                 5
 1
```

<210> 981 <211> 11 ... <212> PRT <213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 981
Asp Asn Thr Ala Trp Tyr Glu Ser Phe Leu Ala
                 5
<210> 982
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 982
Asp Asn Thr Ala Trp Tyr Glu Asn Phe Leu Leu
                 5
<210> 983
<211> 17
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 983
Pro Ala Arg Glu Asp Asn Thr Ala Trp Tyr Asp Ser Phe Leu Ile Trp
                                      10
  1
Cys
<210> 984
<211> 17
<212> PRT
```

<213> Artificial Sequence

```
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 984
Thr Ser Glu Tyr Asp Asn Thr Thr Trp Tyr Glu Lys Phe Leu Ala Ser
                 5
                                    10
Gln
<210> 985
<211> 17
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 985
Ser Gln Ile Pro Asp Asn Thr Ala Trp Tyr Gln Ser Phe Leu Leu His
                                    10
Gly
<210> 986
<211> 17
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 986
Ser Pro Phe Ile Asp Asn Thr Ala Trp Tyr Glu Asn Phe Leu Leu Thr
                   5
```

Tyr

```
<210> 987
 <211> 17
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <400> 987
 Glu Gln Ile Tyr Asp Asn Thr Ala Trp Tyr Asp His Phe Leu Leu Ser
        5
                                    10
 Tyr
 <210> 988
 <211> 17
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <400> 988
 Thr Pro Phe Ile Asp Asn Thr Ala Trp Tyr Glu Asn Phe Leu Leu Thr
                   5
                                     10
 Tyr
  <210> 989
  <211> 17
  <212> PRT
  <213> Artificial Sequence
<220>
  <223> Description of Artificial Sequence: IL-1 ANTAGONIST
        PEPTIDE
  <400> 989
```

```
Thr Tyr Thr Tyr Asp Asn Thr Ala Trp Tyr Glu Arg Phe Leu Met Ser
                  5
                                     10
Tyr
<210> 990
<211> 17
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 990
Thr Met Thr Gln Asp Asn Thr Ala Trp Tyr Glu Asn Phe Leu Leu Ser
                                    10
                  5
Tyr
<210> 991
<211> 17
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 991
Thr Ile Asp Asn Thr Ala Trp Tyr Ala Asn Leu Val Gln Thr Tyr Pro
                                                          15
                                     10
                  5
Gln
<210> 992
<211> 17 ...
<212> PRT
<213> Artificial Sequence
```

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<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 992
Thr Ile Asp Asn Thr Ala Trp Tyr Glu Arg Phe Leu Ala Gln Tyr Pro
                                     10
qaA
<210> 993
<211> 17
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 993
His Ile Asp Asn Thr Ala Trp Tyr Glu Asn Phe Leu Leu Thr Tyr Thr
                                                          15
                                     10
                  5
Pro
<210> 994
<211> 17
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 994
Ser Gln Asp Asn Thr Ala Trp Tyr Glu Asn Phe Leu Leu Ser Tyr Lys
                                     10
                  5
Ala
```

```
<210> 995
 <211> 17
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <400> 995
 Gln Ile Asp Asn Thr Ala Trp Tyr Glu Arg Phe Leu Leu Gln Tyr Asn
                   5
                                     10
 Ala
 <210> 996
 <211> 17
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <400> 996
Asn Gln Asp Asn Thr Ala Trp Tyr Glu Ser Phe Leu Leu Gln Tyr Asn
                                     10
                   5
 Thr
 <210> 997
 <211> 17
  <212> PRT
  <213> Artificial Sequence
  <220>
  <223> Description of Artificial Sequence: IL-1 ANTAGONIST
        PEPTIDE
```

<400> 997

```
Thr Ile Asp Asn Thr Ala Trp Tyr Glu Asn Phe Leu Leu Asn His Asn 1 5 10 15
```

Leu

<210> 998

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<400> 998

His Tyr Asp Asn Thr Ala Trp Tyr Glu Arg Phe Leu Gln Gln Gly Trp

1 5 10 15

His

<210> 999

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:IL-1 ANTAGONIST
 PEPTIDE

<400> 999

Glu Thr Pro Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro 1 5 10 15

Tyr Ala Leu Pro Leu

20

<210> 1000

<211> 21 ...

<212> PRT .

<213> Artificial Sequence

```
<220>
<223> Description of Artificial Sequence:IL-1 ANTAGONIST
      PEPTIDE
<400> 1000
Tyr Ile Pro Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
                                     10
Tyr Ala Leu Pro Leu
           20
<210> 1001
<211> 21
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<400> 1001
Asp Gly Tyr Asp Arg Trp Arg Gln Ser Gly Glu Arg Tyr Trp Gln Pro
                                    10
Tyr Ala Leu Pro Leu
             20
<210> 1002
<211> 10
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<223> At position 1, Xaa=phosphotyrosine
<220>
<223> At position 2, Xaa=naphthylalanine
```

<220>

<223> At position 3, Xaa=phosphotyrosine

<220>
<223> At position 5, Xaa is an azetidine residue

<400> 1002

Xaa Xaa Xaa Gln Xaa Tyr Ala Leu Pro Leu

1 5 10

<210> 1003 <211> 21 <212> PRT <213> Artificial Sequence <220>

Tyr Ala Leu Pro Leu

<210> 1004 <211> 15 <212> PRT <213> Artificial Sequence

<220> <223> At position 10, Xaa=azetidine

<400> 1004
Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 1005

```
<211> 19
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
     PEPTIDE
<400> 1005
Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr Ala Leu Pro Leu Ser
                5
Asp Asn His
<210> 1006
<211> 15
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 10, Xaa=azetidine
<400> 1006
Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr Ala Leu Pro Leu
                  5
<210> 1007
<211> 11
<212> PRT
<213> Artificial Sequence
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
 <220>
 <223> At position 10, Xaa=azetidine
```

<400> 1007

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 1008

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<220>

<223> At position 1, Xaa=acetylated phe

<220>

<223> At position 10, Xaa=azetidine

<400> 1008

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 1009

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<220>

<223> At position 1, Xaa=acetylated phe

<220>

<223> At position 10, Xaa=azetidine

<400> 1009

Phe Glu Trp Thr Pro Gly Trp Tyr Gln Xaa Tyr
1 5 10

<210> 1010

```
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <220>
 <223> At position 1, Xaa=acetylated phe
 <220>
 <223> At position 10, Xaa=azetidine
 <400> 1010
 Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr
                   5
 <210> 1011
 <211> 11
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: IL-1 ANTAGONIST
       PEPTIDE
 <220>
<223> At position 1, Xaa=acetylated phe
 <223> At position 10, Xaa=azetidine
 <400> 1011
 Phe Glu Trp Thr Pro Ala Tyr Trp Gln Xaa Tyr
   1
                    5
 <210> 1012
  <211> 11
  <212> PRT
  <213> Artificial Sequence
  <220>
```

<223> Description of Artificial Sequence: IL-1 ANTAGONIST

PEPTIDE

```
<220>
<223> At position 1, Xaa=acetylated phe

<220>
<223> At position 10, Xaa=azetidine

<400> 1012

Phe Glu Trp Thr Pro Ala Trp Tyr Gln Xaa Tyr

1 5 10
```

Phe Glu Trp Thr Pro Ala Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 1014
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

<220>
<223> At position 10, Xaa=azetidine

<400> 1014

Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 1015

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

<220>

<223> At position 10, Xaa=azetidine

<400> 1015

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 1016

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<220>

<223> At position 10, Xaa=azetidine

<400> 1016

Phe Glu Trp Thr Pro Gly Trp Tyr Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 1017

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: IL-1 ANTAGONIST

PEPTIDE

Tyr Ala Leu Pro Leu 20

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<210> 1018
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE
<220>
<223> At position 1, Xaa=acetylated phe
<220>
<223> At position 10, Xaa=azetidine
```

<400> 1018

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr

1 5 10

<210> 1019 <211> 11 <212> PRT <213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:IL-1 ANTAGONIST PEPTIDE

<220>
<223> At position 1, Xaa=acetylated phe
<220>

<223> At position 10, Xaa=azetidine

<400> 1019

```
Phe Glu Trp Thr Pro Gly Trp Tyr Gln Xaa Tyr 1 5 10
```

<210> 1020

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: IL-1 ANTAGONIST PEPTIDE

<220>

<223> At position 1, Xaa=acetylated phe

<220>

<223> At position 10, Xaa=azetidine

<400> 1020

Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 1021

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<220>

<223> At position 1, Xaa=acetylated phe

<220>

<223> At position 6, D amino acid residue

<220>

<223> At position 10, Xaa=azetidine

<400> 1021

Phe Glu Trp Thr Pro Ala Tyr Trp Gln Xaa Tyr
1 5 10

```
<210> 1022
<211> 11
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 1, Xaa=acetylated phe
<223> At position 6, D amino acid residue
<220>
<223> At position 10, Xaa=azetidine
<400> 1022
Phe Glu Trp Thr Pro Ala Trp Tyr Gln Xaa Tyr
<210> 1023
<211> 11
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: IL-1 ANTAGONIST
      PEPTIDE
<220>
<223> At position 1, Xaa=acetylated phe
<220>
<223> At position 6, D amino acid residue
<220>
<223> At position 10, Xaa=azetidine
<400> 1023
Phe Glu Trp Thr Pro Ala Tyr Tyr Gln Xaa Tyr
                   5
```

```
<210> 1024
<211> 20
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EPO MIMETIC
     PEPTIDE
<400> 1024
Gly Gly Leu Tyr Leu Cys Arg Phe Gly Pro Val Thr Trp Asp Cys Gly
                                                       15
1 . 5
Tyr Lys Gly Gly
<210> 1025
<211> 20
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EPO MIMETIC
      PEPTIDE
Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
                                   10
                  5
 1
 Pro Gln Gly Gly
             20
 <210> 1026
 <211> 20
 <212> PRT
 <213> Artificial Sequence
<220>
 <223> Description of Artificial Sequence: EPO-MIMETIC
      PEPTIDE
```

<400> 1026

```
Gly Gly Asp Tyr His Cys Arg Met Gly Pro Leu Thr Trp Val Cys Lys

1 10 15
```

Pro Leu Gly Gly 20

<210> 1027

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EPO MIMETIC PEPTIDE

<400> 1027

Cys Gly Arg Glu Cys Pro Arg Leu Cys Gln Ser Ser Cys
1 5 10

<210> 1028

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EPO MIMETIC PEPTIDE

<400> 1028

Cys Asn Gly Arg Cys Val Ser Gly Cys Ala Gly Arg Cys
1 5 10

<210> 1029

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EPO MIMETIC PEPTIDE

<400> 1029

```
Val Gly Asn Tyr Met Cys His Phe Gly Pro Ile Thr Trp Val Cys Arg
                                     10
 1
                  5
Pro Gly Gly Gly
<210> 1030
<211> 20
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: EPO MIMETIC
      PEPTIDE
<400> 1030
Gly Gly Val Tyr Ala Cys Arg Met Gly Pro Ile Thr Trp Val Cys Ser
                                     10
                  5
  1
Pro Leu Gly Gly
             20
<210> 1031
 <211> 5
<212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: VEGF ANTAGONIST
      PEPTIDE
 <400> 1031
 Cys Asn Gly Arg Cys
  1
 <210> 1032
 <211> 9
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: TPO MIMETIC
```

<400> 1032
Cys Asp Cys Arg Gly Asp Cys Phe Cys
1 5

<210> 1033

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EPO MIMETIC

<400> 1033

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly
1 10 15

Gly Gly Gly Phe 20

<210> 1034

<211> 26

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EPO MIMETIC

<400> 1034

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly Gly Gly Gly Phe 20 25

<210> 1035

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EPO MIMETIC

Pro Gly Gly

<210> 1036

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EPO MIMETIC

<400> 1036

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln

<210> 1037

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EPO MIMETIC

<400> 1037

Gly Gly Leu Tyr Ala Cys His Met Gly Pro Met Thr Trp Val Cys Gln
1 5 10 15

Pro Leu Arg Gly

<210> 1038

<211> 22 ...

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<220>
<223> Description of Artificial Sequence: EPO MIMETIC
Thr Ile Ala Gln Tyr Ile Cys Tyr Met Gly Pro Glu Thr Trp Glu Cys
Arg Pro Ser Pro Lys Ala
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<210> 1039
<211> 13
<212> PRT
<213> Artificial Sequence
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<400> 1039
Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
<210> 1040
<211> 11
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: EPO MIMETIC
      PEPTIDE
<400> 1040
Tyr Cys His Phe Gly Pro Leu Thr Trp Val Cys
<210> 1041
<211> 12
<212> PRT
<213> Artificial Sequence
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<220>

<223> Description of Artificial Sequence: EPO MIMETIC PEPTIDE

<400> 1041

Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10

<210> 1042

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<400> 1042

Xaa Xaa Xaa Xaa Xaa Xaa Xaa 40

<210> 1043

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<400> 1043

Asp Leu Xaa Xaa Leu

1

5

<210> 1044

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:INTEGRIN BINDING PEPTIDE

<400> 1044

Arg Thr Asp Leu Asp Ser Leu Arg Thr Tyr Thr Leu

1 5 10

<210> 1045

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TNF ANTAGONIST

<400> 1045

Phe Gly Gly Gly Gly Asp Phe Leu Pro His Tyr Lys Asn Thr Ser
1 5 10 15

Leu Gly His Arg Pro 20

<210> 1046

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: TNF ANTAGONIST

<400> 1046

Asp Phe Leu Pro His Tyr Lys Asn Thr Ser Leu Gly His Arg Pro Gly
1 5 10 15

Gly Gly Gly Phe 20

<210> 1047

<211> 21

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<212> PRT
<213> Artificial Sequence
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<223> Description of Artificial Sequence: IL-1 ANTAGONIST
<400> 1047
Phe Gly Gly Gly Gly Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro
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Tyr Ala Leu Pro Leu
             20
<210> 1048
<211> 21
<212> PRT
<213> Artificial Sequence
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<223> Description of Artificial Sequence: IL-1 ANTAGONIST
<400> 1048
Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr Ala Leu Pro Leu Gly
                                    10
Gly Gly Gly Phe
             20
<210> 1049
 <211> 25
 <212> PRT
 <213> Artificial Sequence
 <223> Description of Artificial Sequence: VEGF ANTAGONIST
 <400> 1049
 Phe Gly Gly Gly Gly Val Glu Pro Asn Cys Asp Ile His Val Met
                                      10
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5

Trp Glu Trp Glu Cys Phe Glu Arg Leu

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<210> 1050
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 <213> Artificial Sequence
 <223> Description of Artificial Sequence: VEGF ANTAGONIST
 <400> 1050
 Val Glu Pro Asn Cys Asp Ile His Val Met Trp Glu Trp Glu Cys Phe
                                     10
 Glu Arg Leu Gly Gly Gly Gly Phe
              20
 <210> 1051
 <211> 16
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: MMP INHIBITOR
<400> 1051
 Phe Gly Gly Gly Gly Cys Thr Thr His Trp Gly Phe Thr Leu Cys
                                     10
                   5
 <210> 1052
 <211> 16
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: MMP INHIBITOR
 <400> 1052
 Cys Thr Thr His Trp Gly Phe Thr Leu Cys Gly Gly Gly Gly Phe
                  5
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<210> 1053 <211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: INTEGRIN BINDING PEPTIDE

<400> 1053

Arg Thr Asp Leu Asp Ser Leu Arg Thr Tyr
1 5 10

<210> 1054

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: INTEGRIN BINDING PEPTIDE

<400> 1054

Arg Thr Asp Leu Asp Ser Leu Arg Thr

<210> 1055

<211> 757

<212> DNA

<213> Artificial Sequence

<220>

<220>

<221> CDS

<222> (4)..(747)

<400> 1055

cat atg gac aaa act cac aca tgt cca cct tgt cca gct ccg gaa ctc 48
Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu

1 5 10 15

ctg ggg gga ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc 96 Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr

20 25 30

ctc	atg	atc	tcc	cgg	acc	cct	gag	gtc	aca	tgc	gtg	gtg	gtg	gac	gtg	144
Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Va1	Thr	Cys	Val	Val	Val	Asp	Val	
			35	-				40					45			
agc	cac	gaa	qac	cct	gag	gtc	aag	ttc	aac	tgg	tac	gtg	gac	ggc	gtg	192
-														Gly		
		50					55			-	-	60	_	-		
дад	ata	cat	aat	acc	aaσ	aca	aaq	cca	caa	gag	gag	cag	tac	aac	agc	240
				-										Asn		
	65				-,-	70	-		•		75		-			
	•••	•														
acq	tac	cat	ata	atc	адс	atc	ctc	acc	atc	cta	cac	cag	gac	tgg	ctg	288
_		-												Trp		
80	-,-	5			85		-			90			•	-	95	
					•••											
aat	aac.	ааσ	gag	tac	ааσ	tac	aad	atc	tcc	aac	aaa	acc	ctc	cca	acc	336
														Pro		
	013	<i></i> 10	014	100	٠,٠	0,0	-1-		105		-, -			110		
ccc	atc	gág	aaa	acc	atc	tcc	aaa	acc	aaa	aaa	caq	ccc	cga	gaa	cca	384
														Glu		
110	110		115				-,-	120	-3-				125			
сап	ata	tac	acc	cta	ccc	cca	tcc	caa	gat	gag	cta	acc	aag	aac	cag	432
														Asn		
U 1	***	130					135	3				140	-			
atc	age	cta	acc	tac	cta	atc	aaa	aac	ttc	tat	ccc	agc	gac	atc	gcc	480
														Ile		•
	145			-,-		150	-4-	•		•	155		-			
ata	σασ	taa	gag	agc	aat	gga	cag	cca	gag	aac	aac	tac	aag	acc	acg	528
														Thr		
160					165					170		_			175	
												•				
aat	CCC	ata	ctø	gac	tcc	gac	gac	tcc	ttc	ttc	ctc	tac	agc	aag	ctc	576
Pro	Pro	Val	Leu	Asp	Ser	Asp	Glv	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	
				180					185			_		190		
acc	ata	gac	aad	age	agg	taa	саσ	cad	gaa	aac	gtc	ttc	tca	tgc	tcc	624
Thr	Val	Acn	Lve	Ser	Ara	Trn	Gln	Gln	Glv	Asn	Val	Phe	Ser	Cys	Ser	
- 111 <u>-</u>	-41	ىود	195		7	- - <u>p</u>		200					205			
a+a	a+~	 Cat	asa	act	cta	cac	aac	cac	tac	aco	caq	aag	ago	cto	tcc	672
77=1	Mot	Hie	Glu	Ala	Len	His	Asn	His	Tvr	Thr	Gln	Lys	Ser	Leu	Ser	
ACT	MEC	*****	GIU						-4-			-				

210 215 220

ctg tct ccg ggt aaa ggt gga ggt ggt ggt gac ttc ctg ccg cac tac 720
Leu Ser Pro Gly Lys Gly Gly Gly Gly Asp Phe Leu Pro His Tyr
225 230 235

aaa aac acc tct ctg ggt cac cgt ccg taatggatcc 757
Lys Asn Thr Ser Leu Gly His Arg Pro
240 245

<210> 1056

<211> 248

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence:Fc-TNF-ALPHA INHIBITOR

<400> 1056

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu 1 5 10 15

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu 20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser 35 40 45

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu 50 55 60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr 65 70 75 80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn 85 90 95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro 100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val 130 135 140

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val 145 150 155 160

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr 180 185 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val 195 200 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu 210 215 220

Ser Pro Gly Lys Gly Gly Gly Gly Gly Asp Phe Leu Pro His Tyr Lys 225 230 235 240

Asn Thr Ser Leu Gly His Arg Pro 245

<210> 1057

<211> 761

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:TNF-ALPH INHIBITOR Fc

<220>

<221> CDS

<222> (4)..(747)

<400> 1057

Cat atg gac ttc ctg ccg cac tac aaa aac acc tct ctg ggt cac cgt 48

Met Asp Phe Leu Pro His Tyr Lys Asn Thr Ser Leu Gly His Arg

1 5 10 15

ccg ggt gga ggc ggt ggg gac aaa act cac aca tgt cca cct tgc cca 96
Pro Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro
20 25 30

gca cct gaa ctc ctg ggg gga ccg tca gtt ttc ctc ttc ccc cca aaa 144
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
35 40 45

ccc aag gac acc ctc atg atc tcc cgg acc cct gag gtc aca tgc gtg 192

Pro	Lys	qaA 50	Thr	Leu	Met	Ile	Ser 55	Arg	Thr	Pro	Glu	Val 60	Thr	Сув	Val	
					cac											240
Val	Va1 65	qeA	Val	Ser	His	Glu 70	Asp	Pro	Glu	Val	1 75	Phe	Asn	Trp	Tyr	
					gtg											288
Va1 80	Asp	GIĀ	Val	GIU	Val 85	HIS	ASN	AIA	гуз	90	пув	PIO	Arg	GIU	95	
					tac											336
Gln	Tyr	Asn	Ser	10.0	Tyr	Arg	Val	vaı	105	vaı	rea	Thr	vai	110	nis	
					ggc											384
Gln	Asp	Trp	115	Asn	Gly	Lys	GIU	120	гÀв	Cys	гув	vai	125	ASII	гàя	
					atc											432
Ala	Leu	Pro 130	Ala	Pro	Ile	Glu	Lys 135	Thr	Ile	Ser	Lys	140	Lys	GIĀ	GIN	•
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Pro	Arg 145	Glu	Pro	Gln	Val	Tyr 150	Thr	Leu	Pro	Pro	5er 155	Arg	Asp	GIU	Leu	
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Thr 160	Lys	Asn	Gln	Val	Ser 165	Leu	Thr	Сув	Leu	Val 170	Lys	Gly	Pne	Tyr	175	
agc	gac	atc	gcc	gtg	gag	tgg	gag	agc	aat	ggg	cag	ccg	gag	aac	aac	576
Ser	Asp	Ile	Ala	Val 180	Glu	Trp	Glu	Ser	Asn 185	Gly	Gln	Pro	GIU	190	ASn	٠
tac	aag	acc	acg	cct	ccc	gtg	ctg	gac	tcc	gac	ggc	tcc	ttc	ttc	ctc	624
Tyr	Lys	Thr	Thr 195	Pro	Pro	Val	Leu	Asp 200	Ser	Asp	Gly	Ser	205	Pne	Leu	
tac	agc	aag	ctc	acc	gtg	gac	aag	agc	agg	tgg	cag	cag	ggg	aac	gtc	672
Tyr	Ser	Lys 210		Thr	Val	Asp	Lys 215		Arg	Trp	Gln	Gln 220		Asn	Val	
ttc	tca	tgc	tcc	gtg	atg	cat	gag	gct	ctg	cac	aac	cac	tac	acg	cag	720
Phe	Ser 225	Сув	Ser	Val	Met	His 230	Glu	Ala	Leu	His	Asn 235	His	Tyr	Thr	Gln ~	
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Lys Ser Leu Ser Leu Ser Pro Gly Lys 240 245

<210> 1058

<211> 248

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence:TNF-ALPH INHIBITOR Fc

<400> 1058

Met Asp Phe Leu Pro His Tyr Lys Asn Thr Ser Leu Gly His Arg Pro 1 5 10 15

Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala 20 25 30

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro 35 40 45

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val 50 55 60

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val 65 70 75 80

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln 85 90 95

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
100 105 110

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala 115 120 125

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro 130 135 140

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr 145 150 155 160

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser 165 170 175

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr 180 185 190

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr 195 200 Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe 215 220 Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys 235 230 Ser Leu Ser Leu Ser Pro Gly Lys 245 <210> 1059 <211> 763 <212> DNA <213> Artificial Sequence <223> Description of Artificial Sequence:Fc IL-1 ANTAGONIST <220> <221> CDS <222> (4)..(747) <400> 1059 cat atg gac aaa act cac aca tgt cca cct tgt cca gct ccg gaa ctc Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu 5 ctg ggg gga ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr 25 20 ctc atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val 35 age cae gaa gae eet gag gte aag tte aac tgg tae gtg gae gge gtg Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val 60 - 55 50 gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac agc Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser

70

				gtc Val												288
				tac Tyr 100												336
				acc Thr											-	384
-				ctg Leu												432
				tgc Cys												480
				agc Ser												528
				gac Asp 180												576
				agc Ser												624
				gct Ala												672
ctg Leu	tct Ser 225	ccg Pro	ggt Gly	aaa Lys	ggt Gly	gga Gly 230	ggt Gly	ggt Gly	ggt Gly	ttc Phe	gaa Glu 235	Trp	acc	ccg Pro	ggt Gly	720
				tac Tyr		Leu				tgga	tcc	ctcg	ag			763

<210> 1060-

<211> 248

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence:Fc IL-1
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<400> 1060

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu 1 5 10 15

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu 20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser 35 40 45

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu 50 55 60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr 65 70 75 80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn 85 90 95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro 100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln 115 120 125

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val 130 135 140

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val 145 150 155 160

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro 165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr 180 185 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val 195 200 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu 210 225 220

Ser Pro Gly Lys Gly Gly Gly Gly Phe Glu Trp Thr Pro Gly Tyr

225 230 235 240

Trp Gln Pro Tyr Ala Leu Pro Leu 245

<210> 1061

<211> 757

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: IL-1 ANTAGONIST Fc

<220>

<221> CDS

<222> (4)..(747)

<400> 1061

cat atg ttc gaa tgg acc ccg ggt tac tgg cag ccg tac gct ctg ccg 48

Met Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr Ala Leu Pro

1 5 10 15

ctg ggt gga ggc ggt ggg gac aaa act cac aca tgt cca cct tgc cca 96
Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro
20 25 30

gca cct gaa ctc ctg ggg gga ccg tca gtt ttc ctc ttc ccc cca aaa 144
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
35 40 45

ccc aag gac acc ctc atg atc tcc cgg acc cct gag gtc aca tgc gtg 192
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
50 55 60

gtg gtg gac gtg agc cac gaa gac cct gag gtc aag ttc aac tgg tac 240
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
65 70 75

gtg gac ggc gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag 288
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
80 85 90 95

cag tac aac agc acg tac cgt gtg gtc agc gtc ctc acc gtc ctg cac 336 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His 100 105 110

cag	gac	tgg	ctg	aat	ggc	aag	gag	tac	aag	tgc	aag	gtc	tcc	aac	aaa	384
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	
			115					120					125			
מככ	ctc	cca	acc	ccc	atc	aaa	222	acc	atc	tcc	aaa	acc.	aaa	aaa	cad	432
					Ile											432
ALG	neu		Ala	PLO	TIE	GIU		1111	116	Ser	Lys		uys	GLY	GIII	
		130					135					140				
CCC	cga	gaa	cca	cag	gtg	tac	acc	ctg	CCC	cca	tcc	cgg	gat	gag	ctg	480
Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	
	145					150					155					
acc	aaσ	aac	cag	qtc	agc	cta	acc	tgc	ctg	gtc	aaa	ggc	ttc	tat	ccc	528
					Ser											
160	_, _		42		165			-2-		170		•	•		175	
100					100											
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					gag											376
Ser	Asp	Ile	Ala		Glu	Trp	GIU	ser		GIĀ	GIN	Pro	GIU		ABN	
				180					185					190		
tac	aag	acc	acg	cct	CCC	gtg	ctg	gac	tcc	gac	ggc	tcc	ttc	ttc	ctc	624
Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	
			195					200					205			
								•					•			
tac	aσc	aaσ	ctc	acc	gtg	gac	aag	agc	agg	taa	cag	cag	ggg	aac	gtc	672
					Val											
-1-	001	210	200	****	***	2.00	215		9			220				
		210					217									
												a 2 a	+=0	200	cad	720
					atg											,20
Phe		Суз	Ser	Val	Met		Glu	Ala	Leu	HIS		HIS	туг	Thr	GIn	
	225					230					235					
aag	agc	ctc	tcc	ctg	tct	ccg	ggt	aaa	taai	tggat	cc					757
Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys								
240					245											
													-			
					•											
<210)> 1	062														
	1> 24															
	2> PI															
					quen		, -	_			1 -	NIM P C	ONTO	m		
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	F	C									•					
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5

Met Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr Ala Leu Pro Leu

10

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Gly	Gly	Gly	Gly 20	Gly	qeA	Lys	Thr	His 25	Thr	Cys	Pro	Pro	30	Pro	Ala	
Pro	Glu	Leu 35	Leu	Gly	Gly	Pro	Ser 40	Val	Phe	Leu	Phe	Pro 45	Pro	Lys	Pro	
Lys	Asp 50	Thr	Leu	Met	Ile	Ser 55	Arg	Thr	Pro	Glu	Val 60	Thr	Суз	Val	Val	
Val 65	Asp	Val	Ser	His	Glu .70	Asp	Pro	Glu	Väl	Lys 75	Phe	Asn	Trp	Tyr	Val 80	
Asp	Gly	Val	.Glu	Val 85	His	Asn	Ala	Lys	Thr 90	Lys	Pro	Arg	Glu	G1u 95	Gln	
Tyr	Asn		Thr 100	Tyr	Arg	Val	Val	Ser 105	Val	Leu	Thr	Val	Leu 110	His	Gln	
qaA	Trp	Leu 115	Asn	Gly	Lys	Glu	Tyr 120	Lys	Суз	Lys	Val	Ser 125	Asn	Lys	Ala	
Leu	Pro 130	Ala	Pro	Ile	Glu	Lys 135	Thr	Ile	Ser	ГÀЗ	Ala 140	Lys	Gly	Gln	Pro	
Arg	Glu	Pro	Gln	Val	Tyr 150	Thr	Leu	Pro	Pro	Ser 155	Arg	Asp	Glu	Leu	Thr 160	

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr 185 180

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser 170

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr 200

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe 215 220

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys 240 230 235 225

' Ser Leu Ser Leu Ser Pro Gly Lys 245

165

<210> 1063 <211> 773 <212> DNA <213> Artificial Sequence <220> <223> Description of Artificial Sequence:Fc-VEGF ANTAGONIST <220> <221> CDS <222> (4)..(759) <400> 1063 cat atg gac aaa act cac aca tgt cca ccg tgc cca gca cct gaa ctc Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu 10 ctg ggg gga ccg tca gtt ttc ctc ttc ccc cca aaa ccc aag gac acc Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr 20 25 ctc atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val 40 35 age cae gaa gae eet gag gte aag tte aac tgg tae gtg gae gge gtg Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val 50 55 gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac agc 240 Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser 70 65 acg tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg 288 Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu 95 85 90 80 aat ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala 105 100 ccc atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca 384 Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro 125 120 115

cag gtg tac acc ctg ccc cca tcc cgg gat gag ctg acc aag aac cag Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln

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130 135 140

gtc agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala 150 145 gtg gag tgg gag agc aat ggg cag ccg gag aac aac tac aag acc acg 528 Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr 170 160 165 cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu 180 185 acc gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser 200 205 195 gtg atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc tcc 672 Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser 215 210 ctg tct ccg ggt aaa ggt ggt ggt ggt ggt gtt gaa ccg aac tgt gac Leu Ser Pro Gly Lys Gly Gly Gly Gly Gly Val Glu Pro Asn Cys Asp 235 230 225 atc cat gtt atg tgg gaa tgg gaa tgt ttt gaa cgt ctg taactcgagg 769 Ile His Val Met Trp Glu Trp Glu Cys Phe Glu Arg Leu 245 773 atcc

<210> 1064 <211> 252

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence:Fc-VEGF
 ANTAGONIST

<400> 1064

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu 1 5 10 15

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
20 .25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Asp Val Ser

45

35	40
J.J	70

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu 50 55 60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr 65 70 75 80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn 85 90 95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro 100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val 130 135 140

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val 145 150 155 160

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro 165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr 180 185 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val 195 200 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu 210 215 220

Ser Pro Gly Lys Gly Gly Gly Gly Val Glu Pro Asn Cys Asp Ile
225 230 235 240

His Val Met Trp Glu Trp Glu Cys Phe Glu Arg Leu 245 250

<210> 1065

<211> 773

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: VEGF ANTAGONIST Fc

<220>

<221> CDS

<222> (4)..(759)

<400> 1065

cat atg gtt gaa ccg aac tgt gac atc cat gtt atg tgg gaa tgg gaa 48

Met Val Glu Pro Asn Cys Asp Ile His Val Met Trp Glu Trp Glu

1 5 10 15

tgt ttt gaa cgt ctg ggt ggt ggt ggt ggt gac aaa act cac aca tgt 96
Cys Phe Glu Arg Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys
20 25 30

cca ccg tgc cca gca cct gaa ctc ctg ggg gga ccg tca gtt ttc ctc 144
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
35 40 45

ttc ccc cca aaa ccc aag gac acc ctc atg atc tcc cgg acc cct gag 192
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
50 55 60

gtc aca tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc aag 240
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
65 70 75

ttc aac tgg tac gtg gac ggc gtg gag gtg cat aat gcc aag aca aag 288
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
80 85 90 95

ccg cgg gag gag cag tac aac agc acg tac cgt gtg gtc agc gtc ctc 336
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
100 105 110

acc gtc ctg cac cag gac tgg ctg aat ggc aag gag tac aag tgc aag 384
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
115 120 125

gtc tcc aac aaa gcc ctc cca gcc ccc atc gag aaa acc atc tcc aaa 432 Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys 130 135 140

gcc aaa ggg cag ccc cga gaa cca cag gtg tac acc ctg ccc cca tcc 480
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser

145 150 155

cgg gat gag ctg acc aag aac cag gtc agc ctg a Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu 1 160 165 170	
ggc ttc tat ccc agc gac atc gcc gtg gag tgg c Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp c 180 185	
ccg gag aac aac tac aag acc acg cct ccc gtg c Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val 1 195 200	
tcc ttc ttc ctc tac agc aag ctc acc gtg gac agc ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp 2210 215	
cag ggg aac gtc ttc tca tgc tcc gtg atg cat c Gln Gly Asn Val Phe Ser Cys Ser Val Met His c 225 230	
cac tac acg cag aag agc ctc tcc ctg tct ccg His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro 240 245 250	
atcc	773
<210> 1066 <211> 252	
<212> PRT <213> Artificial Sequence <223> Description of Artificial Sequence:VEG Fc	F ANTAGONIST
<212> PRT <213> Artificial Sequence <223> Description of Artificial Sequence:VEG	
<212> PRT <213> Artificial Sequence <223> Description of Artificial Sequence:VEG Fc <400> 1066 Met Val Glu Pro Asn Cys Asp Ile His Val Met	Trp Glu Trp Glu Cys 15
<212> PRT <213> Artificial Sequence <223> Description of Artificial Sequence:VEG FC <400> 1066 Met Val Glu Pro Asn Cys Asp Ile His Val Met 1 5 10 Phe Glu Arg Leu Gly Gly Gly Gly Gly Asp Lys	Trp Glu Trp Glu Cys 15 Thr His Thr Cys Pro 30

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln 210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro. Gly Lys 245 250

<210> 1067

<211> 748

<212> DNA

<213> Artificial Sequence

<220>

<220>

<221> CDS <222> (4)..(732)

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	1				5					10					15	
					gtc											96
Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	
				20					25					30		
ctc	atg	atc	tcc	cgg	acc	cct	gag	gtc	aca	tgc	gtg	gtg	gtg	gac	gtg	144
Leu	Met	Ile		Arg	Thr	Pro	Glu		Thr	Cys	Vai	Val		ASP	vaı	
			35					40					45			
					gag		227	++~	220	taa	tac	ata	gac	aac	ata	192
agc	cac	gaa	gac	CCL	Glu	g.c	tara	Dhe	Agr	m.r.v	Tur	Val	Asn	Glv	Val	
Ser	HIS		Asp	PIO	GIU	Vai	лу <i>ъ</i> 55	FIIC	Mon	ΙΙĐ	-1-	60		01,		
		50					33									
asa	ata	cat	ast	acc	aag	aca	ааσ	cca	caa	gag	gag	cag	tac	aac	agc	240
Glu	Val	Hig	Agn	Ala	Lys	Thr	Lvs	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	
GIU	65				-2-	70			•		75					
	03															•
acq	tac	cgt	gtg	gtc	agc	gtc	ctc	acc	gtc	ctg	cac	çag	gac	tgg	ctg	288
Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Va1	Leu	His	Gln	Asp	Trp	Leu	
80	_				85					90					95	
aat	ggc	aag	gag	.tac	aag	tgc	aag	gtc	tcc	aac	aaa	gcc	ctc	cca	gcc	336
Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	
				100					105					110		•
																204
ccc	atc	gag	aaa	acc	atc	tcc	aaa	gcc	aaa	ggg	cag	CCC	cga	gaa	CCA	384
Pro	Ile	Glu			Ile	Ser	Lys		Lys	GIĀ	GIN	PLO		GIU	PIO	
			115				•	120					125			
									~a+	~ ~ ~	cta	acc	аад	aac	cag	432
cag	gtg	tac	acc	ctg	CCC	cca	CCC	cgg	yat	gay	T.e.i	Thr	Lvs	Asn	cag Gln	
Gln	Val			Leu	Pro	Pro	135	MIG	veb	914	Dea	140	-1-		Gln	
		130	1				733									
					ata	ato	222	aac	ttc	tat	ccc	agc	gac	ato	gcc	480
gtc	ago	. Cou	mh	. Cyc	T.em	Val	Lvs	Glv	Phe	Tvr	Pro	Ser	Asp	Ile	Ala	
vair	145		1111	Cya	Dea	150		1		- •	155	,				
	143	,														
ata	r gan	r tao	r gad	ו פמר	aat	gaa	cad	cca	gag	aac	aac	: tac	aag	acc	acg	528
Val	Glu	1 L <u>ee</u> 1 Lee	Glu	. Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thi	Thr	
160		<u>B</u>			165					170)				175	

165

160

624

672

748

cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu 185 180 acc gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser 195 200 gtg atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc tcc Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser 215 ctg tct ccg ggt aaa ggt gga ggt ggt tgc acc acc cac tgg ggt Leu Ser Pro Gly Lys Gly Gly Gly Gly Cys Thr Thr His Trp Gly 230 235 225 ttc acc ctg tgc taatggatcc ctcgag Phe Thr Leu Cys 240 <210> 1068 <211> 243 <212> PRT <213> Artificial Sequence <223> Description of Artificial Sequence:Fc-MMP INHIBITOR <400> 1068 Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu 5 10 Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu 25 Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser 45 40 35 His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu 60 55 50 Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr 75 70 65 Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn 90 85 Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val 130 135 140

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro 165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr 180 185 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val 195 200 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu 210 215 220

Ser Pro Gly Lys Gly Gly Gly Gly Cys Thr Thr His Trp Gly Phe 225 230 235 240

Thr Leu Cys

<210> 1069

<211> 763

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:MMP INHIBITOR Fc

<220>

<221> CDS

<222> (4) .. (753)

<400> 1069

Cat atg tgc acc acc cac tgg ggt ttc acc ctg tgc ggt gga ggc ggt

Met Cys Thr Thr His Trp Gly Phe Thr Leu Cys Gly Gly Gly

1 5 10 15

			ggt Gly													96
			cct Pro 35													144
			aag Lys													192
tgc Cys	gtg Val 65	gtg Val	gtg Val	gac Asp	gtg Val	agc Ser 70	cac His	gaa Glu	gac Asp	cct Pro	gag Glu 75	gtc Val	aag Lys	ttc Phe	aac Asn	240
tgg Trp 80	tac Tyr	gtg Val	gac Asp	ggc Gly	gtg Val 85	gag Glu	gtg Val	cat His	aat Asn	gcc Ala 90	aag Lys	aca Thr	aag Lys	ccg Pro	cgg Arg 95	288
gag Glu	gag Glu	cag Gln	tac Tyr	aac Asn 100	agc Ser	acg Thr	tac Tyr	cgt Arg	gtg Val 105	gtc Val	agc Ser	gtc Val	ctc Leu	acc Thr 110	gtc Val	336
ctg Leu	cac His	cag Gln	gac Asp 115	tgg Trp	ctg Leu	aat Asn	ggc Gly	aag Lys 120	gag Glu	tac Tyr	aag Lys	tgc Cys	aag Lys 125	gtc Val	tcc Ser	384
aac Asn	aaa Lys	gcc Ala 130	ctc Leu	cca Pro	gcc Ala	ccc Pro	atc Ile 135	gag Glu	aaa Lys	acc Thr	atc Ile	tcc Ser 140	aaa Lys	gcc Ala	aaa Lys	432
ggg Gly	cag Gln 145	Pro	cga Arg	gaa Glu	cca Pro	cag Gln 150	Val	tac Tyr	acc	ctg Leu	ccc Pro 155	cca Pro	tcc Ser	cgg Arg	gat Asp	480
gag Glu 160	Leu	acc Thr	aag Lys	aac	cag Gln 165	Val	agc Ser	ctg Leu	acc	tgc Cys	Leu	gtc Val	aaa Lys	ggc	Phe	528
tat Tyr	ccc	ago Ser	gac Asp	ato	Ala	gtg Val	gag Glu	tgg Trp	gag Glu 185	Ser	aat Asn	ggg	cag Gln	ccg Pro 190	gag Glu	576
aac	aac Asn	tac Tyr	aag Lys 195	Thr	acq	g cct	ccc Pro	gtç Val	Leu	gac Asp	tcc Ser	gac Asp	ggc Gl ₂ 205	Ser	ttc Phe	624

tto cto tac ago aag oto aco gtg gac aag ago agg tgg cag cag ggg Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly 215 210 aac gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac aac cac tac 720 Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr 230 225 763 acg cag aag agc ctc tcc ctg tct ccg ggt aaa taatggatcc Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys 250 240 245 <210> 1070 <211> 250 <212> PRT <213> Artificial Sequence <223> Description of Artificial Sequence: MMP INHIBITOR FC <400> 1070 Met Cys Thr Thr His Trp Gly Phe Thr Leu Cys Gly Gly Gly Gly 15 5 Asp Lys Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys 25 20 Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro 40 35 Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys 60 55 50 Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp 75 70. Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu 90 Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu 110 100 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn 120 115 Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly 140 135 130

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu 145 150 155 160

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr 165 170 175

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn 180 185 190

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe 195 200 205

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn 210 215 220

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr 225 230 235 240

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys 245 250

<210> 1071

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: INTEGRIN BINDING PEPTIDE

<400> 1071

Cys Gly Arg Glu Cys Pro Arg Leu Cys Gln Ser Ser Cys
1 5 10

<210> 1072

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: INTEGRIN BINDING PEPTIDE

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<400> 1072
Cys Asn Gly Arg Cys Val Ser Gly Cys Ala Gly Arg Cys
                                    10
                 5
<210> 1073
<211> 8
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: INTEGRIN
    BINDING PEPTIDE
<400> 1073
Cys Leu Ser Gly Ser Leu Ser Cys
                 5
<210> 1074
<211> 6
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: INTEGRIN
     BINDING PEPTIDE
<400> 1074
Asn Gly Arg Ala His Ala
 1
             5
<210> 1075
<211> 5
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: INTEGRIN
      BINDING PEPTIDE
<220>
<221> CDS
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<222> (10)..(189)

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<400> 1075
Cys Asn Gly Arg Cys
<210> 1076
<211> 9
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: INTEGRIN
      BINDING PEPTIDE
<400> 1076
Cys Asp Cys Arg Gly Asp Cys Phe Cys
                 5
<210> 1077
<211> 7
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: INTEGRIN
      BINDING PEPTIDE
<400> 1077
Cys Gly Ser Leu Val Arg Cys
                  5
<210> 1078
<211> 8
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: INTEGRIN
      BINDING PEPTIDE
<400> 1078 .
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Arg Thr Asp Leu Asp Ser Leu Arg

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WO 00/24782

1 5

<210> 1079

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:INTEGRIN BINDING PEPTIDE

<400> 1079 .

Gly Asp Leu Asp Leu Leu Lys Leu Arg Leu Thr Leu
1 5 10

<210> 1080

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial
 Sequence:INTEGRIN-BINDING PEPTIDE

<400> 1080

Gly Asp Leu His Ser Leu Arg Gln Leu Leu Ser Arg
1 5 10

<210> 1081

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial
 Sequence:INTEGRIN-BINDING PEPTIDE

<400> 1081

Arg Asp Asp Leu His Met Leu Arg Leu Gln Leu Trp

1 5 10

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<210> 1082
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial
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<400> 1082
Ser Ser Asp Leu His Ala Leu Lys Lys Arg Tyr Gly
                 5
<210> 1083
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial
      Sequence: INTEGRIN-BINDING PEPTIDE
<400> 1083
Arg Gly Asp Leu Lys Gln Leu Ser Glu Leu Thr Trp
  1 . 5
<210> 1084
<211> 12
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial
      Sequence: INTEGRIN-BINDING PEPTIDE
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Arg Gly Asp Leu Ala Ala Leu Ser Ala Pro Pro Val

5

<210> 1085 <211> 15

<400> 1084

1

<212> PRT

<213> Artificial Sequence

<220>

<400> 1085

Asp Phe Leu Pro His Tyr Lys Asn Thr Ser Leu Gly His Arg Pro 1 5 10 15

<210> 1086

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<400> 1086

Gly Glu Arg Trp Cys Phe Asp Gly Pro Leu Thr Trp Val Cys Gly Glu
1 5 10 15

Glu Ser

<210> 1087

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<400> 1087

Arg Gly Trp Val Glu Ile Cys Val Ala Asp Asp Asn Gly Met Cys Val 1 5 10 15

Thr Glu Ala Gln

... 20

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<210> 1088
<211> 19
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VEGF ANTAGONIST
      PEPTIDE
<400> 1088
Gly Trp Asp Glu Cys Asp Val Ala Arg Met Trp Glu Trp Glu Cys Phe
                                                         15
                                     10
                  5
Ala Gly Val
<210> 1089
<211> 16
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: VEGF ANTAGONIST
      PEPTIDE
<400> 1089
Arg Gly Trp Val Glu Ile Cys Glu Ser Asp Val Trp Gly Arg Cys Leu
                                     10
                 5
<210> 1090
<211> 16
 <212> PRT
<213> Artificial Sequence
<220>
 <223> Description of Artificial Sequence: VEGF ANTAGONIST
       PEPTIDE
 <400> 1090
 Arg Gly Trp Val Glu Ile Cys Glu Ser Asp Val Trp Gly Arg Cys Leu
                             . 10
   1
                 5
```

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<210> 1091
<211> 19
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: VEGF ANTAGONIST
      PEPTIDE
<400> 1091
Gly Gly Asn Glu Cys Asp Ile Ala Arg Met Trp Glu Trp Glu Cys Phe
                                     10
Glu Arg Leu
<210> 1092
<211> 16
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: VEGF ANTAGONIST
      PEPTIDE
<400> 1092
Arg Gly Trp Val Glu Ile Cys Ala Ala Asp Asp Tyr Gly Arg Cys Leu
                                     10
                  5
<210> 1093
<211> 8
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: MMP INHIBITOR
      PEPTIDE
<400> 1093
Cys Leu Arg Ser Gly Xaa Gly Cys
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5

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<210> 1094
<211> 10
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: MMP INHIBITOR
     PEPTIDE
<400> 1094
Cys Xaa Xaa His Trp Gly Phe Xaa Xaa Cys
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WO 00/24782

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-Fc PCR PRIMER

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	Description of Artificial Sequence:Fc PCR PRIMER	
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Ala Ala Arg Ala
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(19) World Intellectual Property Organization International Bureau



(43) International Publication Date 4 May 2000 (04.05.2000)

PCT

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(26) Publication Language:

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(30) Priority Data:

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- (74) Agents: ODRE, Steven, M. et al.; Amgen, Inc., One Amgen Center Drive. Thousand Oaks, CA 91320-1799 (US).

- (81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW). Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- (88) Date of publication of the international search report: 6 June 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



(54) Title: MODIFIED PEPTIDES, COMPRISING AN FC DOMAIN, AS THERAPEUTIC AGENTS

(57) Abstract: The present invention concerns fusion of Fc domains with biologically active peptides and a process for preparing pharmaceutical agents using biologically active peptides. In this invention, pharmacologically active compounds are prepared by a process comprising: a) selecting at least one peptide that modulates the activity of a protein of interest; and b) preparing a pharmacologic agent comprising an Fc domain covalently linked to at least one amino acid of the selected peptide. Linkage to the vehicle increases the half-life of the peptide, which otherwise would be quickly degraded *in vivo*. The preferred vehicle is an Fc domain. The peptide is preferably selected by phage display, *E. coli* display, ribosome display, RNA-peptide screening, or chemical-peptide screening.

ational Application No

PCT/US 99/25044 A. CLASSIFICATION OF SUBJECT MATTER IPC 7 CO7K19/00 C12N C12N15/70 C12N15/62 C12N1/21 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07K A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) BIOSIS, EMBASE, WPI Data, PAJ, EPO-Internal, STRAND C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Category ° Relevant to claim No. X WO 98 46257 A (AMGEN INC.) 1-3,5-722 October 1998 (1998-10-22) page 3, line 12 -page 4, line 4 page 12, line 9 - line 25 Y 11-21,51 X WO 96 18412 A (BETH ISRAEL HOSPITAL 1-3,5,6, ASSOCIATION) 20 June 1996 (1996-06-20) 22-24 page 8, line 14 -page 12, line 26 claims X Further documents are listed in the continuation of box C. Patent family members are listed in annex. Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international
- "L" document which may throw doubts on priority clarm(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of mailing of the international search report

Date of the actual completion of the international search

18 October 2000

Authorized officer

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Fax: (+31-70) 340-3016

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07 12 2000

Int .tional Application No PCT/US 99/25044

C (Ca-a)	POCUMENTO COMPLETE DO COMPLETE DE COMPLETE	PCT/US 99/25044
C.(Continua Category °	ation) DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages	
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'	page 13, Time 27 page 14, Time 3	10,11, 26-29, 34,35, 40-51
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	page 10, line 31 -page 11, line 13 page 22, line 10 - line 35	
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	WO 97 44453 A (GENENTECH INC.) 27 November 1997 (1997-11-27) examples claims	1-6, 22-2 4
'		36
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'	the whore document	37
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	figure 1	37
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	-/	

Inte Vional Application No PC1/US 99/25044

	TS CONSIDERED TO BE RELEVANT nent, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Category * Citation of docum	nent, with indication, where appropriate, of the relevant passages	Relevant to claim No.
16 June seq.id.	7 234 A (YANOFSKY ET AL.) 1998 (1998-06-16) nos. 10,17,46,259 8, line 54 - line 57	10
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		12-17,33
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tional application No. PCT/US 99/25044

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet) This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons: Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: 2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically: Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet) This International Searching Authority found multiple inventions in this international application, as follows: see additional sheet As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.: No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: The additional search fees were accompanied by the applicant's protest. Remark on Protest No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-7 (partially), 8-11 (completely), 22-32 (partially), 35 (completely), 39-51 (partially)

17

Compositions of matter of the formula (X1)a-F1-(X2)b and multimers thereof, wherein F1 is an Fc domain, X1 and X2 are each independently selected from -(L1)c-P1, -(L1)c-P1-(L2)d-P2, -(L1)c-P1-(L2)d-P2-(L3)e-P3, and -(L1)c-P1-(L2)d-P2-(L3)e-P3-(L4)f-P4. P1, P2, P3 and P4 are each independently sequences of pharmacologically activbe peptides; L1, L2, L3 and L4 are each independently linkers, and a, b, c, d and e are each independently 0 or 1, provided that at least one of a and b is 1; DNA encoding said composition, an expression vector comprising said DNA, a host cell comprising said expression vector, Proces for preparing a pharmacologically active compound, and wherein X1 and X2 comprise an IL-1 antagonist peptide sequence.

2. Claims: 1-7 (partially), 12-17 (completely), 22-32 (partially), 33 (completely), 39-51 (partially)

As in subject 1, but wherein X1 and X2 comprise an EPO-mimetic peptide sequence.

3. Claims: 1-7 (partially), 18-21 (completely), 22-32 (partially), 34 (completely), 39-51 (partially)

As in subject 1, but wherein P1 is a TP0-mimetic peptide sequence

4. Claims: 26-32 (partially), 36 (completely), 39-51 (partially)

Process for preparing a pharmacologically active compound, which comprises selecting at least one randomized peptide that modulates the activity of a protein of interest, and preparing a pharmacologic agent comprising one Fc domain covalently linked to at least one amino acid sequence of the selected peptide(s); wherein said peptide is an MMP inhibitor peptide or a VEGF antagonist peptide.

5. Claims: 26-32 (partially), 37 (completely).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

39-51 (partially)

As in subject 4, but wherein said peptide is a TNF antagonist peptide. $\,$

6. Claims: 26-32 (partially), 38 (completely), 39-51 (partially)

As in subject 4, but wherein said peptide is a CTLA4 mimetic peptide.

page 2 of 2

ormation on patent family members

Interr-*Ional Application No PC+, US 99/25044

		1		7 77/25044
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Search

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ID:

Document JP 10-130149 A2

TNF PRODUCTION INHIBITOR Title:

SANKYO CO LTD Assignee:

UBE IND LTD

UCHIYAMA HIROKO Inventor:

KURAKATA SHINICHI NISHIGAKI TAKASHI KIMURA TOMIO

KATSUBE TETSUTSUGU

US Class:

Int'l Class: A61K 31/495 A; C07D 215/56 -; C07D 401/04 -; C07D 401/12 -; C07D 401/14 -; C07D 405/12 -; C07D 409/12 -; C07D 413/12 -;

C07D 413/14 -; C07D 417/12 -; C07D 417/14 -; C07D 471/04 -; C07D 498/04 -; C07D 498/06 -; C07D 498/14 -; C07D 513/04 -;

C07D 513/06 -; C07D 513/14 -; A61K 31/47 B; A61K 31/50 B; A61K 31/505 B; A61K 31/535 B; A61K 31/55 B

Issue Date: 05/19/1998 07/08/1997 Filing

Date:

Abstract:

PROBLEM TO BE SOLVED: To obtain a TNF-α production inhibitor useful as a treating agent for various diseases caused by excess production of the TNF-α by including at least one kind of specific three kinds of quinolonecarboxylic acids as an active ingredient.

SOLUTION: This TNF-α production inhibitor includes at least one kind of quinolonecarboxylic acid of formulas I, II and III {X is H or a halogen; Y is X, a 1-4C alkyl, etc.; Z is a (protected) COOH, etc.; Q is N, a group of formula IV [R2 is H, a 1-4C alkyl (substituted by a halogen), etc.]; W is O or S; T is a 1-4C alkylene (substituted by a 1-4C alkyl), etc.; R1 is H, a 1-4C alkyl (substituted by OH, etc.), etc.; R is a group of formula V [R3 is a 6-10C arly (substituted by nitro, etc.), etc.; R4 and R5 are each H or a 1-4C alkyl; (n) is 1 or 2], etc.} The compound of formulas I, II or III is produced by a method written in a laid open patent application of EP572,259 (Japan laid open patent application 6-116241) and/or a patent of WO/02512, or a method corresponding to these methods.

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Email Link:

Document ID: JP 10-147531 A2

Title:

TNF-ALPHA PRODUCTION INHIBITOR

Assignee:

OTSUKA PHARMACEUT CO LTD

Inventor:

NAGAI HIROKAZU

US Class:

Int'l Class:

A61K 31/47 A; C07D 401/12 -; A61K 31/47

Issue Date:

06/02/1998

Filing Date:

11/19/1996

Abstract:

PROBLEM TO BE SOLVED: To obtain the subject production inhibitor useful as a preventive and a therapeutic agent for chromic rheumatoid arthritis, burn, myocardial infarction, etc., comprising a specific tetrazolylalkoxycarbostyril derivative (salt) as an active ingredient.

SOLUTION: At least one of a tetrazolylalkoxycarbostyril derivative (salt) of the formula (R is a cycloalkyl; A is a lower alkylene; the bond between the 3-position and the 4-position of carbostyril skeleton is a single bond or a double bond) is contained as an active ingredient to give a TNF(Tumor Necrosis Factor)-α production inhibitor. The compound of the formula is made into a dosage form such as tablet or injection by optionally using a conventional preparation carrier and administered. A dose is 100-400mg/day in adult (50kg weight) and preferably administered by dividing into once to several times a day.

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Email Link:

Document ID:

JP 10-231285 A2

Title:

PHTHALIMIDE DERIVATIVE OR ITS SALT, THEIR PRODUCTION AND PHARMACEUTICAL COMPOSITION

CONTAINING THE DERIVATIVE

Assignee:

ISHIHARA SANGYO KAISHA LTD

HASHIMOTO YUICHI

Inventor:

HASHIMOTO YUICHI

US Class:

Int'l Class:

C07D 209/48 A; A61K 31/40 B; A61K 31/42 B; A61K 31/435 B; C07D 209/44 B; C07D 209/46 B; C07D 413/04 B; C07D 413/06

B; C07D 471/04 B

Issue Date:

09/02/1998

Filing Date:

09/25/1997

Abstract:

PROBLEM TO BE SOLVED: To obtain the subject new compound producible by reacting a specific dialdehyde compound with an amine compound and subjecting the product to salt-forming reaction and useful e.g. as an active component of a pharmaceutical composition for controlling the production of tumor necrosis factor inducing various diseases.

SOLUTION: This new phthalimide derivative (salt) is expressed by formula I [X is =CY- (Y is H, nitro, amino, cyano, CF3, OH, a halogen or an alkyl) or =N-Y; Z1 and Z2 are each O or S; (1) is 1, 2 or 3; (m) and (n) are each 0 or 1; Q1 and Q2 are each H or an alkyl; R is a (substituted)biphenyl or a (substituted)indanyl], e.g. 2-(3,5-dimethylisoxazol-4-ylmethyl)-4,5,6,7-tetrafluoro-1H-isoindol-1,3-dione. The compound is useful e.g. as an agent for controlling the production of tumor necrosis factor. The compound can be produced by reacting a dialdehyde compound of formula II with an amine compound of formula III and optionally subjecting the product to salt-forming reaction.

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Email Link:

Document ID: JP 10-259140 A2

Title: TUMOR NECROTIZING FACTOR PRODUCTION INHIBITOR

Assignee: SUMITOMO PHARMACEUT CO LTD

Inventor: KAWARAI HIROKO

KOIKE HARUHIKO TOJO SHINICHIRO

US Class:

Int'l Class: A61K 39/395 A; C07H 07/027 -; A61K 39/395 B; A61K 31/70 B

Issue Date: 09/29/1998 **Filing Date:** 03/18/1997

Abstract:

PROBLEM TO BE SOLVED: To obtain the subject inhibitor useful for treatment of dyscrasia, septicemia, multiple organ failure, etc., by including anti-selektin antibody or sugar binding with the selektin.

SOLUTION: The objective preparation is obtained by formulating anti- selektin antibody (anti-P-selektin antibody, e.g. mouse antihuman-P-selektin monoclonal antibody PB1.3) or a sugar binding with the selektin (sialyl-Lewis X and sialyl-Lewis X derivative, Lewis X and Lewis X derivative, especially preferably the one including α 1,3-fucosylated α 2,3-sialated lactosaminoglycan structure) with a conventional pharmaceutical carrier and an auxiliary material. The objective preparation is used for treating or preventing a disease, the appearance of which is considered to be corresponding to TNF through a production inhibition of the TNF by the sugar. An daily dose of the objective preparation is generally about 0.5mg-2000mg per patient of 70kg body weight.

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Email Link:

Document ID: JP 10-316570 A2

Title: TNF-ALPHA INDUCTIVE EFFECT INHIBITOR

Assignee: DAI ICHI SEIYAKU CO LTD

Inventor: BABA MASANORI

IKEUCHI KIYOSHI KIMURA YOICHI

US Class:

Int'l Class: A61K 31/495 A; C07D 215/56 -; C07D 401/04 -; C07D 401/14 -; A61K 31/47

В

Issue Date: 12/02/1998 **Filing Date:** 05/13/1997

Abstract:

PROBLEM TO BE SOLVED: To obtain a medicine capable of inhibiting effects, such as those of disorders associated with inflammation induced by TNF-α (tumor necrosis factor) and those of gene expression suppression by HIV, by including a carboxylic acid derivative as an active ingredient.

SOLUTION: This inhibitor comprises a compound or its salt of the formula [R1 is a 1-6C alkyl, halogen, aryl, etc.; R2 is H, 1-6C alkylthio, etc.; R3 is H, amino, a halogen, etc.; R4 and R6 is H, a 1-6C alkyl; R5 is a halogen, 1-6C alkyl, etc.; X is H or a halogen; A is N or C-R7 (R7 is H, a halogen, etc.); (m) is 2 or 3; Y is OH or O-R8 (R8 is phenyl, etc.); (z) is C or N]. The compound of the formula is effective for the treatment of chronic rheumatoid arthritis, septic shock, ulcerative colitis, etc., and suppression of development of AIDS caused by accelerated replication and transcription of HIV gene.

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JP 11-001481 A2

ID: Title:

PIPERIDINYLPHTHALAZINE DERIVATIVE

Assignee:

SUMITOMO PHARMACEUT CO LTD

Inventor:

FUJITA ICHIJI

MURATA SHINOBU KAWAKAMI HAJIME

US Class:

Int'l Class:

C07D 401/04 A; A61K 31/50 B; A61K 31/505 B; C07D 401/14 B; C07D 405/14 B; C07D 409/14 B; C07D 413/14 B; C07D

417/14 B

Issue Date:

01/06/1999 06/10/1997

Filing Date:

Abstract:

PROBLEM TO BE SOLVED: To obtain the subject new compound, having inhibiting actions on the production or secretion of a tumor necrosis factor and useful as a therapeutic agent for cachexia, spetic shocks, multiple organ failure, chronic articular rheumatism, inflammatory intestinal diseases, etc.

SOLUTION: This compound is represented by formula I (R1 to R5 are each H, a halogen, an alkyl, etc.; R6 is an aryl, etc.; R7 is H, an aryl, etc.), e.g. 1-[4-(2-dithienylmethylene)piperidino]phthalazine. The compound represented by formula I is obtained by reacting a phthalazine derivative represented by formula II (X is a halogen) with a pieridine derivative represented by formula III in an inert organic solvent at 0-200°C and providing a halogenated piperidinylphthalazine derivative represented by formula IV which affords a compound included in the compound represented by formula I in which the R1 is the halogen. The resultant compound represented by formula IV is then hydrogenated in the presence of a catalyst to provide the compound represented by formula I in which R1 is the H. The compound is effective even in treating multiple sclerosis, arthrosis deformans. Behcet's disease, systemic lupus erythematosus, rejection and the time of bone marrow transplantation, malaria, AIDS, etc., besides the diseases described above.

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